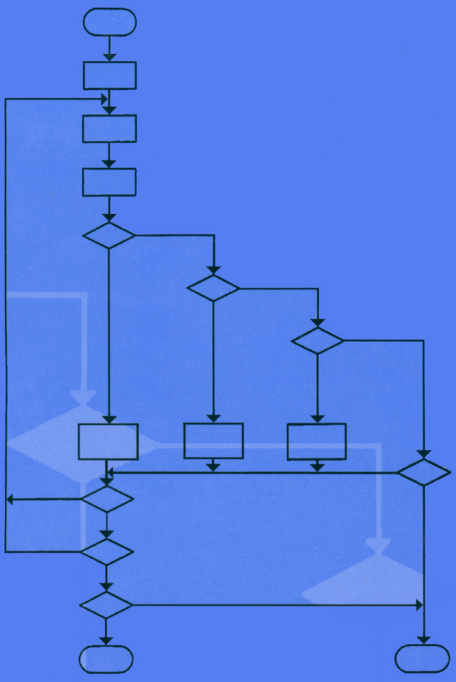
Medical Device Quality Assurance and Regulatory Compliance



Richard C. Fries

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To

Helen Grenier

whose lifelong committment to education

has been a constant inspiration

Preface

Medical device manufacturers establish and follow quality systems to ensure their products are safe, effective, and reliable for their intended use and consistently meet applicable specifications and requirements. To assist the manufacturer in this goal, standards for quality systems have been established worldwide. In addition, individual countries or groups of countries have developed regulations that must be met prior to importing a product to that country.

In the United States, the quality systems for products regulated by the Food and Drug Administration (FDA) are known as the Quality System regulation. In addition, the Safe Medical Devices Act of 1990 provided FDA with the authority to add preproduction design controls to the regulations. The FDA has also enacted regulations regarding submission of data prior to making a device available in the marketplace.

Internationally, the ISO 9000 series addresses quality systems for all manufacturers. Working group 1 of ISO Technical Committee 210 has developed standards (ISO 13485 and ISO 13488), which apply ISO 9001 to medical devices. EN 46000 is a European standard that specifically addresses medical devices. Recently, the ISO 14000 series of standards were published to address environmental issues for all manufacturers.

In 1992, the Global Harmonization Task Force (GHTF) was formed in an effort to harmonize regulatory requirements for the medical device industry. The GHTF consists of representatives for the Canadian Ministry of Health and Welfare, the Japanese Ministry of Health and Welfare, the FDA, industry members from the European Union, Australia, Canada, Japan, the United States, and a few delegates from observing countries.

The world of quality assurance and regulatory compliance can be one of confusion and bewilderment. This book attempts to give some direction to the medical device manufacturer so that compliance activity becomes a standard part of the product development process. The primary goal of this text is to acquaint the developer of medical devices with the basic concepts and major issues of medical quality assurance and regulatory documents, to describe the requirements listed in these documents, and to provide strategies for compliance to these requirements. To achieve this goal, this book is divided into 5 sections.

Section 1 is an overview of the various quality assurance and regulatory requirements. It discusses the history of the FDA, the European Economic Community, and the Global Harmonization Task Force.

Section 2 discusses in detail the quality system standards. The ISO 9000 series of standards is reviewed, followed by an in-depth discussion of each requirement, and a strategy for meeting those requirements. Discussions include choosing a standard from the series, getting the company ready for the auditor, choosing a notified body, and surviving the audit. Section 2 concludes with a discussion of the ISO 14000 series of standards in the same depth.

While Section 2 looked at the process, Section 3 investigates the product. Standards are discussed that deal specifically with medical devices, including EN 46000, ISO 13485, and ISO 13488. EN 46000 is a standard that addresses the product development process. After an overview of the standard, this section looks at the individual requirements of the standard and then discusses a strategy for meeting those requirements. ISO 13485 and 13488 are recent standards developed to address ISO 9001 requirements for medical devices. Many in Europe suggest that eventually, these documents will replace EN 46000. The requirements of ISO 13485 and 13488 are examined in detail, followed by a strategy for compliance.

Section 4 deals with Regulatory compliance. Each of the Medical Device Directives is discussed, followed by a detailed discussion of requirements and a strategy for compliance. This is followed by a similar discussion of the new Quality System Regulation requirements and the

requirements for product submittals prior to product introduction. These discussions will include current issues the FDA is attempting to deal with, including third party approvals.

Section 5 consists of various appendices listing standards organizations, Quality System registrars/Notified Bodies, regulatory agencies, various FDA offices, consultants and training organizations, and testing organizations. The final appendix is a glossary of terms.

Knowledge of the quality assurance and regulatory requirements is an essential part of every medical device development process. Being able to comply with the requirements is essential to the financial success of the manufacturer. It is hoped this text will be an invaluable resource in establishing standards and regulatory compliance as a vital part of every medical device manufacturer's operation.

I am deeply indebted to many people for their encouragement, help, and constructive criticism in the preparation of this book. I want to thank Tina Juneau and Chuck Morreale who reviewed the chapters and provided fresh insight. I want to thank Eric Stannard at Marcel Dekker, Inc., whose expertise and humor made the job of editing this book tolerable. Mostly, I want to thank my wife, June, who constantly encouraged me and who sacrificed much quality time during the preparation and editing that we otherwise would have spent together.

Richard C. Fries

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Section 1

Standards and Regulations Background

Chapter 1

Quality Assurance and Regulatory Compliance

As a result of revolutionary changes that have occurred around the world, we are part of an inevitable phenomenon: globalization of the economy. Internationalization of competition, deregulation of world trade, the boom of the information economy, and the management revolution move more and more companies to change the way they do business, the way they think, and the way they manage. They are adapting to the new reality to ensure their present survival and future prosperity. Many are reconfiguring their organizations and adopting new political, technical, and cultural values. Business leaders are revolutionizing their management thinking and implementing strategic information management, total quality management, empowerment, reengineering, policy deployment, cross-functional management, activity-based management, and environmental management. Quality may be the biggest competitive issue of the new century.

1.1 Quality Assurance

At the start of this century, mass production and the evolution of technology quickly rendered unit inspection costly, ineffective, or inapplicable. This period was marked by the birth of statistical sampling for inspection and acceptance of the product at receiving and shipping. This inspection method,

based on attributes that permit classification of lots as good or bad, did not preclude the delivery of a certain percentage of defective products to the buyer. In 1924, at Bell Laboratories in the United States, Walter Shewhart invented the control chart as a tool for measuring process variations. In general, these statistical control methods were limited to process control and to product inspection, and served to detect non-quality.

In the 1950s, the United States introduced a new procurement concept in the military sector. Instead of gathering enough qualified inspectors to examine large quantities of goods or parts that were physically impossible to inspect, Department of Defense (DOD) experts advocated quality assurance by establishing the MIL-Q-9858 standard. For the first time in history, this quality program detailed contractual specifications for procurement. In the early 1960s, this contractual philosophy appeared in the United Kingdom in the Polaris program.

During this period, quality assurance was focused on the supplier. The idea consisted not only of inspecting parts, but of assuring that the supplier was perfectly organized. To implement this idea, purchasers required a set of preventive measures and evidence of their application from suppliers before ordering. However, the quality assurance field lacked clear distinctions and definitions of concepts such as inspection, quality control, statistical control, internal and external quality assurance, quality management, and total quality management.

Today, businesses are changing from the mass production model to the mass customization model and quality assurance is focused on the customer. This renewed concept consists of establishing guidelines, measures, and rules within a quality system that encompasses the majority of a company's activities. The key is to prevent, detect, and resolve problems of non-quality with trained employees and to demonstrate the effectiveness of the chosen measure in order to attract customer satisfaction. Quality Assurance includes inspection and statistical quality controls as a means of detection and sometimes even as a prevention tool. Quality management, as fine-tuned by quality leaders such as W. Edward Deming, Joseph Juran, and Kaoru Ishikawa, consists in the company elaborating its own quality policy and vision for customer satisfaction. Quality management requires-top leadership commitment and a customer-focused approach that goes far beyond a service of quality assurance. In constant evolution, this concept has developed into Total Quality Management (TQM). It integrates the employees', the customers', and the owners' satisfaction while also respecting the environment and society.

1.2 Regulation

Medical devices are an extraordinarily heterogeneous category of products. The term *medical device* includes such technologically simple articles as ice bags and tongue depressors. On the other end of the spectrum, very sophisticated articles such as pacemakers and surgical lasers are also medical devices. Perhaps it is this diversity of products coupled with the sheer number of different devices that makes the development of an effective and efficient regulatory scheme a unique challenge for the Congress and the Food and Drug Administration (FDA) in the United States and the European Commission (EC) in Europe.

1.2.1 Regulation in the United States

Historically, medical devices have been neglected from a legislative and regulatory perspective. In the early 1900s, Congressional attention focused on food and drugs. The Pure Food and Drug Act of 1906 was passed to prohibit the distribution of adulterated or misbranded food and drugs to interstate commerce. This legislation, however, did not include any provisions to enable the Food and Drug Administration to regulate medical devices. Thus, legitimate and fraudulent medical devices were freely marketed without any effective check on the safety of these articles or the accuracy of their claims.

The most significant rationale for authorizing the FDA to regulate medical devices was the mounting level of consumer fraud. In the years preceding the Federal Food, Drug, and Cosmetic Act of 1938, medical devices were marketed that touted false therapeutic claims. Many of these devices were patently harmful. Others, by virtue of their bogus therapeutic claims, delayed consumers from seeking proper medical attention. Thus, a growing concern evolved - the public welfare was in jeopardy unless a mechanism was established to regulate the safety and reliability of medical devices.

It was not until 1938, when the Pure Food and Drug Act of 1906 underwent extensive revision, that the Congress expressly empowered the federal government to regulate medical devices. The Federal Food, Drug and Cosmetic Act of 1938 expanded the FDA's regulatory control over food and drugs and extended the agency's authority to include medical devices and cosmetics.

The FDA's regulatory authority over medical devices remained unchanged until the mid-1970s. In the late 1960s and early 1970s, there was some interest expressed by administrative officials and members of Congress in improving the regulatory framework for medical devices. Although some of this interest culminated in device regulation bills, formal legislation was not enacted until May, 1976. The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, of 1976, established an intricate statutory framework to enable the FDA to regulate nearly every aspect of medical devices, from testing through marketing.

1.2.2 Regulation in Europe

The European Community's program on the completion of the Internal Market has, as the primary objective for medical devices, to ensure Community-wide free circulation of products. The only means to establish such free circulation, in view of quite divergent national systems, regulations governing medical devices, and existing trade barriers, was to adopt legislation for the Community, by which the health and safety of patients, users, and third persons would be ensured through a harmonized set of device related protection requirements. Devices meeting the requirements and sold to members of the Community are identified by means of a CE mark.

Because of the diversity of current national medical device standards, attempts to introduce mutual recognition of device approvals to reconcile the different regimes proved to be fruitless. The European Commission eventually decided that totally new EC legislation, covering all medical devices was needed.

The Active Implantable Medical Devices Directive adopted by the Community legislator in 1990 and the Medical Devices Directive in 1993 cover more than 80% of medical devices for use with human beings. The In-Vitro Diagnostic Medical Devices Directive, which came into force in 1997, addresses the remaining devices. After a period of transition, i.e., a period during which the laws implementing a Directive co-exist with pre-existing national laws, these directives exhaustively govern the conditions for placing medical devices on the market. Through the agreements on the European Economic Area (EEA), the relevant requirements and procedures are the same for all European Community member states and European Free Trade Association (EFTA) countries that belong to the EEA, an economic area comprising more than 380 million people.

1.3 Standards

The degree to which formal standards and procedures are applied to product development varies from company to company. In many cases, standards are dictated by customers or regulatory mandate. In other situations, standards are self-imposed. If formal standards do exist, an assurance activity must be established to guarantee that they are being followed. An assessment of compliance to standards may be conducted as part of a formal technical review or by audit.

Standards simplify communication, promote consistency and uniformity, and eliminate the need to invent yet another solution to the same problem. They are a way of preserving proven practices above and beyond the inevitable staff changes within organizations. Standards, whether official or merely agreed upon, are especially important when talking to customers and suppliers, but it is easy to underestimate their importance when dealing with different departments and disciplines within our own organization.

1.3.1 Standards in the United States

Standards are important in that they impact our industry in many ways. Most of the standards activity relevant to the medical device, diagnostic product, and health care information systems industry, falls into one or more of the four following types:

- regulatory
- national voluntary consensus
- foreign national
- international.

Regulatory standards are those that generally have some basis in law. National voluntary standards are the work products of groups. Foreign national standards are like our own national regulatory and voluntary standards except that they are for other countries. International standards are the attempts by countries to try to reduce the differences in national standards through organizations such as the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).

People who work on medical device standards have been conditioned to think only in terms of voluntary and regulatory standards. While that may be a useful distinction in law, in practice, the distinctions blur because most standards fit into a gray area. From a practical point of view it does not matter

very much if a standard is labeled mandatory or voluntary. There are examples of regulatory agency standards being promoted as guidelines and voluntary standards being used as mandatory requirements.

The American National Standards Institute's (ANSI) 1987 *Summary Annual Report of Medical Device Standards Board Activities* identifies over 700 voluntary medical device standards completed or under development. These standards cover everything from needles, syringes, and thermometers to diagnostic test kits, electrical safety, and laboratory computers. Some of these standards are clearly defined and cover only a specific device. Others, however, are so broad - on sterilization, for example - that they cover whole classes of medical devices.

1.3.1.1 Software Standards

There are a myriad of software standards to assist the developer in designing and documenting his program. The Institute of Electrical and Electronic Engineers' (IEEE) standards cover documentation through all phases of design. Military standards describe how software is to be designed and developed for military use. There are also standards on software quality and reliability to assist developers in preparing a quality program. The international community has produced standards, primarily dealing with software safety. In each case, the standard is a voluntary document that has been developed to provide guidelines for designing, developing, testing, and documenting a software program.

In the United States, the FDA is responsible for assuring the device utilizing software or the software as a device is safe and effective for its intended use. The FDA has produced several drafts of reviewer guidelines, auditor guidelines, software policy, and Quality System regulations addressing both device and process software. In addition, guidelines for FDA reviewers have been prepared as well as training programs for inspectors and reviewers. The Quality System Regulation addresses software as part of the design phase.

The United States is ahead of other countries in establishing guidelines for medical software development. There is, however, movement within several international organizations to develop regulations and guidelines for software and software controlled devices. For example, ISO 9000-3, *Quality management and quality assurance standards - Part 3: Guidelines for the application of ISO 9001 to the development, supply and maintenance of software,* specifically addresses software development in addition to what is

contained in ISO 9001. The Canadian Standards Association (CSA) addresses software issues in four standards covering new and previously developed software in critical and non-critical applications. IEC has a software document currently in development.

1.3.2 International Standards

Internationally, standards may be defined as:

> A technical specification or other document available to the public, drawn up with the cooperation and consensus or general approval of all interests affected by it, based on the consolidated results of science, technology and experience, aimed at the promotion of optimum community benefits and approved by a body on the national, regional, or international level.

While this definition goes some way to saying what a standard is, it says nothing about the subject matter or purpose, apart from stating that the objectives of the standard must in some way be tied to community benefits.
Standards, however, have a definite subject matter. They include:

- to standardize particular processes,
- to provide a consistent and complete definition of a commodity or process,
- to record good practice regarding the development process associated with the production of commodities,
- to encode good practice for the specification, design, manufacture, testing, maintenance, and operation of commodities.

One of the primary requirements of a standard is that it be produced in such a way that conformance to the standard can be unambiguously determined. A standard is devalued if conformance can not be easily determined or if the standard is so loosely worded that it becomes a matter of debate and conjecture as to whether the requirements of the standard have been met.

Standards also exist in various types:

- De facto and de jure standards. These are usually associated with the prevailing commercial interests in the

market place. These de facto standards are often eventually subject to the standardization process.

- Reference models. These provide a framework within which standards can be formulated.
- Product versus process standards. Some standards relate to specific products while others relate to the process used to produce products.
- Codes of practice, guidelines, and specifications. These terms relate to the manner in which a standard may be enforced. Codes of practice and guidelines reflect ways of working that are deemed to be *good* or *desirable*, but for which conformance is difficult to determine. Specifications are far more precise and conformance can be determined by analysis or test.
- Prospective and retrospective standards. It is clearly undesirable to develop a standard before the subject matter is well understood scientifically, technically, and through practice. However, it may be desirable to develop a standard alongside the evolving technology.

1.4 Coping with Increased Quality Assurance and Regulatory Issues

A manufacturer has several options available for coping with a changing QA and regulatory environment. These range from participating in shaping the new standards and regulations, to responding to them upon completion. Ignoring them is not considered a viable option.

It is important for manufacturers to be involved in the development process for a new standard or regulation. By being part of the process, they can minimize the impact of the new requirements on their development of a product. They can also present knowledgeable inputs to the discussion, based on experience, that will make the standard or regulation more effective.

Standards and regulatory agencies are very keen to inputs from those subject to the standard or regulation. Agencies are interested in developing good working relationships with organizations that are affected by their rules and regulations. It is in the interest of both parties to develop standards and regulations that are meaningful, effective, and do not present an extraordinary burden.

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Chapter 2

The FDA

Regulation of medical devices is intended to protect consumer's health and safety by attempting to ensure that marketed products are effective and safe. Prior to 1976, the FDA had limited authority over medical devices under the Food, Drug, and Cosmetic Act of 1938. Beginning in 1968, Congress established a radiation control program to authorize the establishment of standards for electronic products, including medical and dental radiology equipment. From the early 1960s to 1975, concern over devices increased and six United States Presidential messages were given to encourage medical device legislation.

In 1969, the Department of Health, Education, and Welfare appointed a special committee (the Cooper Committee) to review the scientific literature associated with medical devices. The Committee estimated that over a 10 year period, 10,000 injuries were associated with medical devices, of which 731 resulted in death. The majority of problems were associated with three device types: artificial heart valves, cardiac pacemakers, and intrauterine contraceptive devices. There activities culminated in passage of the Medical Devices Amendments of 1976.

Devices marketed after 1976 are subject to full regulation unless they are found substantially equivalent to a device already on the market in 1976. By the end of 1981, only about 300 of the 17,000 products submitted for clearance to the FDA after 1976 had been found not substantially equivalent.

2.1 History of the FDA

In 1906, the Food and Drug Administration enacted its first regulations addressing public health. While these regulations did not address medical devices per se, they did establish a foundation for future regulations. It was not until 1938, with the passage of the Federal Food, Drug and Cosmetic Act (FFD&C) that the FDA was authorized, for the first time, to regulate medical devices. This act provided for regulation of adulterated or misbranded drugs, cosmetics, and devices that were entered into interstate commerce. A medical device could be marketed without being federally reviewed and approved.

In the years following World War II, the FDA focused much of the attention on drugs and cosmetics. Over-the-counter drugs became regulated in 1961. In 1962, the FDA began requesting safety and efficacy data on new drugs and cosmetics.

By the mid-1960s, it became clear that the provisions of the FFD&C Act were not adequate to regulate the complex medical devices of the times to ensure both patient and user safety. Thus, in 1969, the Cooper Committee was formed to examine the problems associated with medical devices and to develop concepts for new regulations.

In 1976, with input from the Cooper Committee, the FDA created the Medical Device Amendments to the FFD&C Act, which were subsequently signed into law. The purpose of the amendments was to ensure that medical devices were safe, effective, and properly labeled for their intended use. To accomplish this mandate, the amendments provided the FDA with the authority to regulate devices during most phases of their development, testing, production, distribution, and use. This marked the first time the FDA clearly distinguished between devices and drugs. Regulatory requirements were derived from this 1976 law.

In 1978, with the authority granted the FDA by the amendments, the Good Manufacturing Practices (GMP) were promulgated. The GMP represents a quality assurance program intended to control the manufacturing, packaging, storage, distribution, and installation of medical devices. This regulation was

intended to allow only safe and effective devices to reach the market place. It is this regulation that has the greatest effect on the medical device industry. It allows the FDA to inspect a company's operations and take action on any noted deficiencies, including prohibition of device shipment.

Recent regulations specific to medical devices are the Medical Device Reporting (MDR) regulation of 1984, the Device Reconditioner/Rebuilder (DRR) regulation of 1988, the Safe Medical Devices Act of 1992, and the Quality System Regulation of 1997.

2.2 Registration and Listing

Under Section 510 of the FFD&C Act, every person engaged in the manufacture, preparation, propagation, compounding, or processing of a device shall register their name, place of business and such establishment. This includes manufacturers of devices and components, repackers, relabelers, as well as initial distributors of imported devices. Those not required to register include manufacturers of raw materials, licensed practitioners, manufacturers of devices for use solely in research or teaching, warehousers, manufacturers of veterinary devices, and those who only dispense devices, such as pharmacies.

Upon registration, the FDA issues a device registration number. A change in the ownership or corporate structure of the firm, the location, or person designated as the official correspondent must be communicated to the FDA device registration and listing branch within 30 days. Registration must be done when first beginning to manufacture medical devices and must be updated yearly.

Section 510 of the FFD&C Act also requires all manufacturers to list the medical devices they market. Listing includes not only informing the FDA of products manufactured, but also providing the agency with copies of labeling and advertising. Listing must be done when first beginning to manufacture a product. Device listing need to be updated when one or more of the following occurs:

- a device is introduced into commercial distribution with a classification name not currently listed with the FDA
- the intended use of a listed device changes in such a way that would result in its being more appropriately classified under a different classification name
- the marketing of all devices having the same classification name is discontinued by the company

- a commercial distribution of devices identified by a previously discontinued classification name is resumed by the company
- a change occurs in the owner or operator, registration number, establishment name, or establishment type.

Foreign firms that market products in the United States are permitted but not required to register, and are required to list. Foreign devices that are not listed are not permitted to enter the country.

Registration and listing provides the FDA with information about the identity of manufacturers and the products they make. This information enables the agency to schedule inspections of facilities and also to follow up on problems. When the FDA learns about a safety defect in a particular type of device, it can use the listing information to notify all manufacturers of those devices about that defect.

2.3 Device Classification

A medical device is any article or health care product intended for use in the diagnosis of disease or other condition or for use in the care, treatment, or prevention of disease that does not achieve any of its primary intended purposes by chemical action or by being metabolized.

From 1962, when Congress passed the last major drug law revision, and first attempted to include devices, until 1976 when device laws were finally written, there were almost constant congressional hearings. Testimony was presented by medical and surgical specialty groups, industry, basic biomedical sciences, and various government agencies, including the FDA. All of the viewpoints and arguments that we hear today were proposed, and considered in public discussion. Nearly two dozen bills were rejected as either inadequate or inappropriate.

The Cooper Committee concluded that the many inherent and important differences between drugs and devices necessitated a regulatory plan specifically adapted to devices. They recognized that some degree of risk is inherent in the development of many devices. They also realized that:

- all hazards cannot be eliminated
- there is often little or no prior experience on which to base judgments about safety and effectiveness

- that devices undergo performance improvement modifications during the course of clinical trials
- that results also depend upon the skill of the user.

They therefore rejected the drug-based approach and created a new system for evaluating devices. All devices were placed into classes based upon the degree of risk posed by each individual device and its intended use. The Pre-Market Notification Process (510(k)) and the Pre-Market Approval Application (PMAA) became the regulatory pathways for device approval. The Investigational Device Exemption (IDE) became the mechanism to establish safety and efficacy in clinical studies for PMAAs.

2.3.1 Class I Devices

Class I devices were defined in 1976 as non-life sustaining devices, whose failure posed no risk to life, and thus required no need for performance standards. Basic standards, however, such as premarket notification (510(k)), registration, device listing, good manufacturing practices (GMP), and proper record keeping are all required. Nonetheless, the FDA has exempted many of the simpler Class I devices from some or all of these requirements. For example, tongue depressors and stethoscopes are both Class I devices; both are exempt from GMP, tongue depressors are exempt from 510(k) filing, whereas stethoscopes are not.

2.3.2 Class II Devices

Class II devices were also defined as non-life sustaining devices. However, they must not only comply with the basic standards for Class I devices, but must meet specific controls or performance standards. For example, sphygmomanometers, although not essential for life, must meet standards of accuracy and reproducibility. Class II devices must also have premarket notification information submitted prior to marketing.

Premarket notification is documentation submitted by a manufacturer that notifies the FDA that a device is about to be marketed. It assists the agency in making a determination about whether the device is "substantially equivalent" to a previously marketed predecessor device. As provided for in section 510(k) of the Food, Drug, and Cosmetic Act, the FDA can clear a device for marketing on the basis of premarket notification that the device is substantially equivalent to a pre-1976 predecessor device. The decision is based on premarket

notification information that is provided by the manufacturer including the intended use, physical composition, specifications of the device, and risk analysis. Additional data usually submitted includes environmental testing, verification and validation results, and compatibility studies.

The premarket notification or 510(k) process was designed to give manufacturers the opportunity to obtain rapid market approval of these noncritical devices by providing evidence that their device is "substantially equivalent" to a device that is already marketed. The device must have the same intended use and the same or equally safe and effective technological characteristics as a predicate device.

The Safe Medical Device Act of 1990 and the Amendments of 1992 attempted to take advantage of what had been learned since 1976. The regulations gave both the FDA and manufacturers greater leeway by permitting down-classification of many devices, including some life supporting and life sustaining devices previously in Class III. This was based on the fact that reasonable assurance of safety and effectiveness could be obtained by application of "Special Controls" such as performance standards, post market surveillance, guidelines, and patient and device registries.

2.3.3 Class III Devices

Class III devices were defined in 1976 as either sustaining or supporting life so that their failure is life threatening. For example, heart valves, pacemakers and PCTA balloon catheters are all Class III devices. Class III devices almost always require a PMAA, a long and complicated task fraught with many pitfalls, that has caused the greatest confusion and dissatisfaction for both industry and the FDA.

The new regulations permit the FDA to use data contained in four prior PMAs for a specific device, that demonstrate safety and effectiveness, to approve future PMA applications by establishing performance standards or actual reclassification. Composition and manufacturing methods which companies wish to keep as proprietary secrets are excluded. Advisory Medical panel review is now elective.

However, for PMAAs that continue to be required, all of the basic requirements for Class I and II devices must be provided, plus failure mode analysis, animal tests, toxicology studies, and then finally human clinical studies, directed to establish safety and efficacy under an IDE.

It is necessary that preparation of the PMA must actually begin years before it will be submitted. It is only after the company has the results of all of the laboratory testing, pre-clinical animal testing, failure mode analysis and manufacturing standards on their final design, that their proof of safety and efficacy can begin, in the form of a clinical study under an IDE.

At this point the manufacturer must not only have settled on a specific, fixed design for his device, but with his marketing and clinical consultants must also have decided on what the indications, contraindications, and warnings for use will be. The clinical study must be carefully designed to support these claims.

Section 520(g) of the Federal Food, Drug, and Cosmetic Act, as amended, authorizes the FDA to grant an IDE to a researcher using a device in studies undertaken to develop safety and effectiveness data for that device when such studies involve human subjects. An approved IDE application permits a device that would otherwise be subject to marketing clearance to be shipped lawfully for the purpose of conducting a clinical study. An approved IDE also exempts a device from certain sections of the Act. All new significant risk devices not granted substantial equivalence under the 510(k) section of the Act must pursue clinical testing under an IDE.

An Institutional Review Board (IRB) is any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of the review is to ensure the protection of the rights and welfare of human subjects. Any human research covered by federal regulation will not be funded unless it has been reviewed by an IRB. The fundamental purpose of an IRB is to ensure that research activities are conducted in an ethica and legal manner. Specifically, IRBs are expected to ensure that each of the basic elements of informed consent, as defined by regulation, are included in th document presented to the research participant for signature or verbal approval.

2.4 Medical Device Submissions

Medical device submissions may be of separate types:

- 510(k)
- Premarket Approval (PMA)
- Investigational Device Exemption (IDE).

Under section 510(k) of the Federal Food, Drug, and Cosmetic Act, a person who intends to introduce a device into commercial distribution is required to submit a premarket notification, or 510(k), to the FDA at least 90 days before commercial distribution is to begin. The FDA may then issue an order of substantial equivalence, only upon making a determination that the device to be introduced into commercial distribution is as safe and effective as a legally marketed device.

Premarket Approval (PMA) is an approval application for a Class III medical device, including all information submitted with or incorporated by reference. The purpose of the regulation is to establish an efficient and thorough device review process to facilitate the approval of PMAs for devices that have been shown to be safe and effective for their intended use and that otherwise meet the statutory criteria for approval, while ensuring the disapproval of PMAs for devices that have not been shown to be safe and effective or that do not otherwise meet the statutory criteria for approval.

The purpose of the Investigational Device Exemption (IDE) regulation is to encourage the discovery and development of useful devices intended for human use while protecting the public health. It provides the procedures for the conduct of clinical investigations of devices. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with a performance standard or having marketing clearance.

2.5 Medical Device Reporting

On July 31, 1996, the new Medical Device Reporting (MDR) regulation became effective for user facilities and device manufacturers. The MDR regulation provides a mechanism for the Food and Drug Administration and manufacturers to identify and monitor significant adverse events involving medical devices. The goals are to detect and correct problems in a timely manner. Although the requirements of the regulation can be enforced through legal sanctions authorized by the Federal Food, Drug and Cosmetic Act, FDA relies on the goodwill and cooperation of all affected groups to accomplish the objectives of the regulation.

The statutory authority for the MDR regulation is section 519 of the FD&C Act as amended by the Safe Medical Devices Act (SMDA) of 1990. The SMDA requires user facilities to report:

- device-related deaths to the FDA and the device manufacturer,

- device-related serious injuries and serious illnesses to the manufacturer, or to FDA if the manufacturer is not known,
- submit to FDA on a semiannual basis a summary of all reports submitted during that period.

2.6 Quality System Regulation

Current good manufacturing practice requirements are set forth in the Quality System Regulation of 1996. The requirements govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act by establishing basic requirements applicable to manufacturers of finished medical devices. The regulation establishes for the first time design control requirements. The format of the regulation is very similar to that of ISO 9001.

The regulation is applicable to any finished device intended for human use that is manufactured, imported, or offered for import in any state or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

The regulation went into effect June 1, 1997. A grace period has been granted until June 14, 1998, the same day the grace period for the Medical Device Directives ends. During the grace period, the FDA may inspect a manufacturer's facilities to the Quality System Regulation, but may not list any findings on the form 483 or bring sanctions against a manufacturer for non-compliances to the Quality System Regulation.

2.7 The FDA Inspection

The FDA's power to inspect originates in Section 704 of the Federal Food, Drug, and Cosmetic Act. This provision allows FDA officials to inspect any factory, warehouse, or establishment in which devices are manufactured, processed, packed or held, for introduction into interstate commerce of after such introduction. In addition to the "establishments" specification, FDA is permitted to enter any vehicle used to transport or hold regulated products for export or in interstate commerce. The inspection power is specifically extended to medical device manufacturers by Sections 519 and 520 of the Federal Food, Drug, and Cosmetic Act.

Every FDA inspector is authorized by law to inspect all equipment that is used in the manufacturing process. Furthermore, investigators may examine finished and unfinished devices and device components, containers, labeling for regulated products, and all documents that are required to be kept by the regulations, such as device master records and device history records.

Despite the broad inspectional authority over restricted devices, the statute provides that regardless of the device's unrestricted status, certain information is excluded from FDA's inspectional gambit. The kind of information to which FDA does not have access includes financial data, sales data, and pricing data. The new Quality System Regulation, released in 1996, gives the FDA authority to inspect the design area and the qualifications of personnel in all aspects of the product development process.

2.8 A Look at the Future

Reform is inevitable at the FDA. There are signs that Congress will pass the first serious FDA-downsizing federal budget and possibly make its final move on separate FDA reform legislation. Facing serious budgetary cuts, the FDA is looking at alternative methods of operation. Some suggested reforms include:

- Shifting the reviewer force from low-risk device 510(k)s to PMA applications, pre-1976 devices, and device reclassification. The result would be timelier reviews while maintaining scientific rigor.
- Diverting reviewers from lower-risk devices to the more technically complex 510(k) submissions that usually require clinical data. The remaining devices could be farmed out to external reviews or exempted from 510(k) review altogether. Another possibility is self-certification or third-party certification that the devices conform to recognized consensus standards or self-certification by the manufacturer that their devices conform to the FDA's design control requirement.
- Reforming medical device reporting (MDR) management to make greater use of summaries and electronic filing. Thus fewer people would be needed to shuffle paper.
- Reducing the number of routine inspections and focusing on compliance inspections and for-cause (enforcement) inspections.

Not only is the FDA considering these procedural economies, but it is also trying to reengineer the way it does business, in order to afford greater efficiency while retaining a high level of consumer protection.

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Chapter 3

The European Union

The drive toward the creation of a single European economic entity began in 1957 with the signing of the Treaty of Rome. In 1986, the Single European Act established the goal of achieving a single market by 1992 to include 12 member states and approximately 350 million people. Common legislation, the so-called European Directives, were scheduled to cover the entire market. The intention of the European Community (EC) 1992 process was to streamline the approval process for products marketed in the 12 member states. Conceivably, the five member nations of the European Free Trade Association would also recognize the European Directives, even though these nations do not belong to the new common market.

Nearly 300 European Commission Directives have been approved to support implementation of a unified internal market. These directives are not detailed, but rather contain information regarding general *essential requirements.* European regional standards setting bodies are responsible for establishing the voluntary standards, which elaborate on the essential requirements.

The European Union was known as the European Community until the Maastricht Treaty took effect in 1993. Present members include:

Austria
Belgium
Denmark
Finland
France
Germany
Greece
Ireland
Italy
Luxembourg
The Netherlands
Portugal
Spain
Sweden
The United Kingdom.

In 1994, the Agreement on a European Economic Area took effect, adding Iceland, Liechtenstein, and Norway to the single market, although they did not join the European Union. These 18 countries comprise a market approximately the size of the North American Free Trade Agreement.

Standards serve as an essential component in assuring the complete freedom of trade in merchandise across national borders. Standard bodies in the member states are obliged to adopt European standards and withdraw conflicting national standards. Harmonized, European-wide standards in key product sectors are now replacing the thousands of differing national standards that existed within member states. Today, the European standardization system has almost 5,000 standards and produces approximately five new standards per working day.

3.1 European Directives

In the period up to 1992, and subsequently, the European Parliament has enacted a series of measures intended to put the single market into practice. Some of these directives have been aimed at removing barriers of a purely customs/excise nature, while others have concentrated on transport arrangements to ensure the free movement of goods. A series of directives, produced under the heading of "New Approach Directives," are intended to provide controls on product design, with the principal objective being to provide a level playing field for product safety requirements across the European Union.

The primary function of these directives is to ensure that products are sufficiently well designed and built to be fit for the purpose for which they are sold, and that reasonable precautions are taken to protect the user against injury while the product is being used. Recent directives have included provisions for medical devices and electromagnetic compatibility.

In the past, the European Union relied on harmonized legislation to enforce common production standards, without reference to voluntary standards or a marking system. Under this old approach, directives contained such a high degree of detail on the technical specifications of products, it sometimes required a decade or more to complete the technical work.

Now, the new approach directives specify only the *essential requirements* to be met by products and that the technical specifications governing the production and marketing of products meeting the essential requirements be laid down by the relevant European standardization bodies.

3.2 European Standardization Bodies

Under this approach, the European Commission mandated that the private sector be responsible for development of European technical standards. Three regional standards organizations were assigned the task:

- The European Committee for Standardization (CEN),
- The European Committee for Electrotechnical Standardization (CENELEC),
- The European Telecommunications Standards Institute (ETSI).

CEN, CENELEC, and ETSI constitute a European forum for standardization that organizes participation of all parties concerned in the development and standardization programs. These parties include national government authorities, the Commission of European Communities (commonly known as the European Commission) the European Free Trade Association, public bodies, manufacturers, trade unions, users, and consumers. These parties come together in hundreds of technical groups to prepare European standards through procedures that guarantee respect for the principles of openness and transparency, consensus, national commitment, technical coherence at the national and European level, and correct integration with other international work. Consequently, the development of standards within the national bodies of the European Union essentially ceased and work was transferred into the European standards organizations.

Many multinational manufacturers have globalized their product development efforts. Until recently, they have regarded the FDA as the agency with the most experience in regulating medical devices. The EC 1992 process splits the burden of stringent regulation between the United States and the European Commission. Many of these multinational manufacturers have grown accustomed to dealing with U.S. bureaucracy, but now will have to work also with the incipient EC bureaucracy in Brussels. Unraveling the complex European process is extremely difficult. Change is rapid and what is established as fact this week, may be overturned or obsolete next week.

These complex changes and the bureaucracy being created in Brussels are being driven by seven major groups of organizations. The groups consist of the following:

- the European Commission,
- standing committees,
- standards organizations,
- Notified Bodies,
- Board of Health,
- Ethical Committee.

The European Commission, one of the three major branches of the European government, is the primary force of change. Another branch, the European Parliament, debates the directives proposed by the Commission. The third branch, the Court of Justice, will adjudicate any differences that arise between parties within the European Community.

The three medical device directives create standing committees, which after the European Commission, constitute the second major force behind the European regulatory changes. Each directive creates two committees, which could be combined into one major standing committee that would address differences between essential requirements outlined in all the directives and international or European normalized standards. The second standing committee, which might vary depending upon the directive, would address specific issues relevant to that directive. What have been termed *competent authorities*, namely the boards of health of the 12 member states, constitute another major force behind these changes.

Notified Bodies compose yet another force for change. In reality, these are the test houses that are designated by individual member states' board of health. Some states may have more than one test house, and smaller countries

may have none. Those member states that do not designate a Notified Body will delegate their medical device issues to member states that have larger and more resourceful boards of health and Notified Bodies.

Ethical committees at EC medical institutions also play an important role in evaluating investigational devices. Many European teaching institutions already have ethics committees properly constituted and duly functioning. Many non-teaching institutions, however, do not have such committees and will be required to form them.

These organizational forces are, and will remain, highly interactive. Many institutions are working diligently at what they perceive to be their mandate. From the United States perspective, the European process is producing a great deal of activity and, in some cases, significant action. It is clear that many organizations are working to change the legislative and regulatory environment for medical devices in Europe.

3.3 European Standards Development Process

Through their standardization work, CEN, CENELEC, and ETSI aim to remove any differences of a technical nature, either between the national standards of the member states or between measures applied at the national level to certify conformity, that could give rise to technical barriers to trade. In the areas of technology, European Standards are prepared following specific requests from the European Commission and the European Free Trade Association.

3.3.1 New Work

The Dresden Agreement, between CENELEC and IEC, gives IEC the "Right of First Refusal" for work proposed in CENELEC. According to the Vienna Agreement, CEN must determine whether it is possible to give preference to ISO to develop a new project, noting that a completed standards project must be available within specific timeframes. ISO has three months to respond to any such request received from CEN. CEN must also consider its various procedural options and, if the CEN technical committee decides to propose the work item to ISO, work will commence following the normal procedures in one of the following scenarios:

- new work falling within the scope of an existing ISO technical committee and subcommittee