Guidance for Industry and FDA

Regulation of Medical Devices: Background Information for International Officials

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This document supersedes document, "Regulation of Medical Devices: Background Information for Foreign Officials," May l996

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

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Division of Small Manufacturers Assistance
Office of Health and Industry Programs

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Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Ron Parr, Division of Small Manufacturers Assistance, HFZ-220, 1350 Piccard Drive, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Ron Parr by FAX at 30l-443-8818 or by email: rpp@cdrh.fda.gov.

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Regulation of Medical Devices: Background Information for International Officials[1]

This document contains guidance on the basic regulatory requirements that all manufacturers and importers must consider when they plan to market medical devices. It is intended to assist foreign governments in understanding the overall mission of FDA, as well as the FDA regulations for marketing and exporting medical devices to the United States. It is important to know these requirements, how to determine which ones are pertinent to a given situation, and the proper sequence for fulfilling them. It contains guidance on establishment registration, device listing, labeling requirements, classification, premarket notification [510(k)], medical device reporting, and good manufacturing practices of significance to manufacturers and importers of medical devices. This guidance incorporates changes required by the Food and Drug Administration Modernization Act of 1997.

This guidance is intended to replace the document, "Regulation of Medical Devices: Background Information for Foreign Officials," dated May l996.

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Agency.

[1] This guidance document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

PART I.

FOOD AND DRUG ADMINISTRATION (FDA)

STRUCTURE AND FUNCTIONS

The Food and Drug Administration: An Overview

The Food and Drug Administration touches the lives of virtually every American every day. First and foremost, FDA is a public health agency, charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic Act and several related public health laws. It is FDA's job to see that the food we eat is safe and wholesome, the cosmetics we use won't hurt us, the medicines and medical devices we use are safe and effective, and that radiation-emitting products, such as microwave ovens, won't do us harm. Feed and drugs for pets and farm animals also come under FDA scrutiny. FDA also ensures that all of these products are labeled truthfully with the information that people need to use them properly.

FDA is one of our nation's oldest consumer protection agencies. Its approximately 9,000 employees monitor the manufacture, import, transport, storage and sale of $1 trillion worth of products each year. It does that at a cost to the taxpayer of about $3 a person.

To carry out this mandate of consumer protection, FDA has some 1,100 investigators and inspectors who cover the country's almost 95,000 FDA-related businesses. These employees are located in district and local offices in 157 cities across the country.

Inspections and Legal Sanctions

FDA's investigators and inspectors visit more than 15,000 facilities a year, seeing that products are made right and labeled truthfully. As part of their inspections, they collect about 80,000 domestic and imported product samples for examination by FDA scientists or for label checks.

If a company violates any of the laws that FDA enforces, FDA can encourage the firm to voluntarily correct the problem or to recall a faulty product from the market. A recall is generally the fastest and most effective way to protect the public from an unsafe product.

When a company can't or won't correct a public health problem with one of its products voluntarily, FDA has legal sanctions it can bring to bear. The agency can go to court to force a company to stop selling a product and to have items already produced seized and destroyed. When warranted, FDA may seek criminal penalties-including prison sentences-against manufacturers and distributors.

About 3,000 products a year are found to be unfit for consumers and are withdrawn from the marketplace, either by voluntary recall or by court-ordered seizure. In addition, about 30,000 import shipments a year are detained at the port of entry because the goods appear to be unacceptable.

Scientific Expertise

The scientific evidence needed to back up FDA's legal cases is prepared by the agency's 2,100 scientists, including 900 chemists and 300 microbiologists, who work in 40 laboratories in the Washington, D.C. area and around the country. Some of these scientists analyze samples to see, for example, if products are contaminated with illegal substances. Other scientists review test results submitted by companies seeking agency approval for drugs, vaccines, food additives, coloring agents and medical devices.

FDA also operates the National Center for Toxicological Research at Jefferson, Arkansas, which investigates the biological effects of widely used chemicals. The agency also runs the Engineering and Analytical Center at Winchester, Massachusetts, which tests medical devices, radiation-emitting products, and radioactive drugs.

Assessing risks and, for drugs and medical devices, weighing risks against benefits is at the core of FDA's public health protection duties. By ensuring that products and producers meet certain standards, FDA protects consumers and enables them to know what they're buying. For example, the agency requires that drugs, both prescription and over-the-counter, be proven safe and effective.

In deciding whether to approve new drugs, FDA does not itself do research, but rather examines the results of studies done by the manufacturer. The agency must determine that the new drug produces the benefits it's supposed to without causing side effects that would outweigh those benefits.

Product Safety

Another major FDA mission is to protect the safety and wholesomeness of food. The agency's scientists test samples to see if any substances, such as pesticide residues, are present in unacceptable amounts. If contaminants are identified, FDA takes corrective action. FDA also sets labeling standards to help consumers know what is in the foods they buy.

The nation's food supply is protected in yet another way as FDA sees that medical feeds and other drugs given to animals raised for food are not threatening to the consumer's health.

The safety of the nation's blood supply is another FDA responsibility. The agency's investigators routinely examine blood bank operations, from record-keeping to testing for contaminants. FDA also ensures the purity and effectiveness of biologicals (medical preparations made from living organisms and their products), such as insulin and vaccines.

Medical devices are classified and regulated according to their degree of risk to the public. Devices that are life-supporting, life-sustaining or implanted, such as pacemakers, must receive agency approval before they can be marketed.

FDA's scrutiny does not end when a drug or device is approved for marketing; the agency collects and analyzes tens of thousands of reports each year on drugs and devices after they have been put on the market to monitor for any unexpected adverse reactions.

Cosmetic safety also comes under FDA's jurisdiction. The agency can have unsafe cosmetics removed from the market. The dyes and other additives used in drugs, foods, and cosmetics are also subject to FDA scrutiny. The agency must review and approve these chemicals before they can be used.

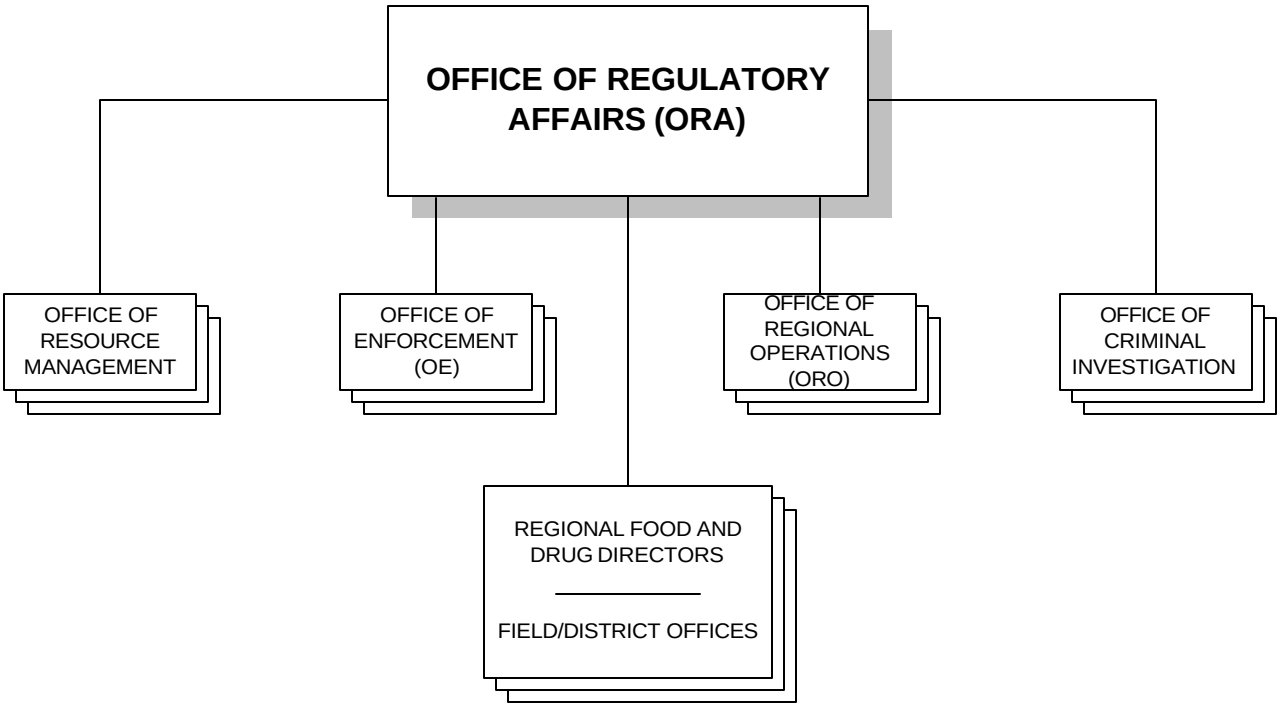
Office of Regulatory Affairs (ORA)

FDA is a scientifically based law enforcement agency. Its enforcement activities are coordinated by ORA, whose function is twofold: to safeguard the public health and to ensure honesty and fair dealing between the regulated industry and consumers.

- FDA encourages and expects compliance with the laws and regulations it enforces. To this end, the agency participates in cooperative and educational efforts designed to inform industry, health professionals, and the public of those legal requirements.

- FDA surveys and inspects regulated industry to assess compliance and discover noncompliance. Depending upon the nature of non-compliance, FDA may afford an opportunity for correction by industry. If adequate correction does not occur within a reasonable period, FDA is committed to swiftly initiating action to obtain compliance. Legal remedies include injunction, seizure and prosecution.

- FDA does not tolerate fraud, intentional violations, or gross negligence, and promptly seeks prosecution to punish and deter whenever appropriate.



ORA's Office of Regional Operations (ORO)

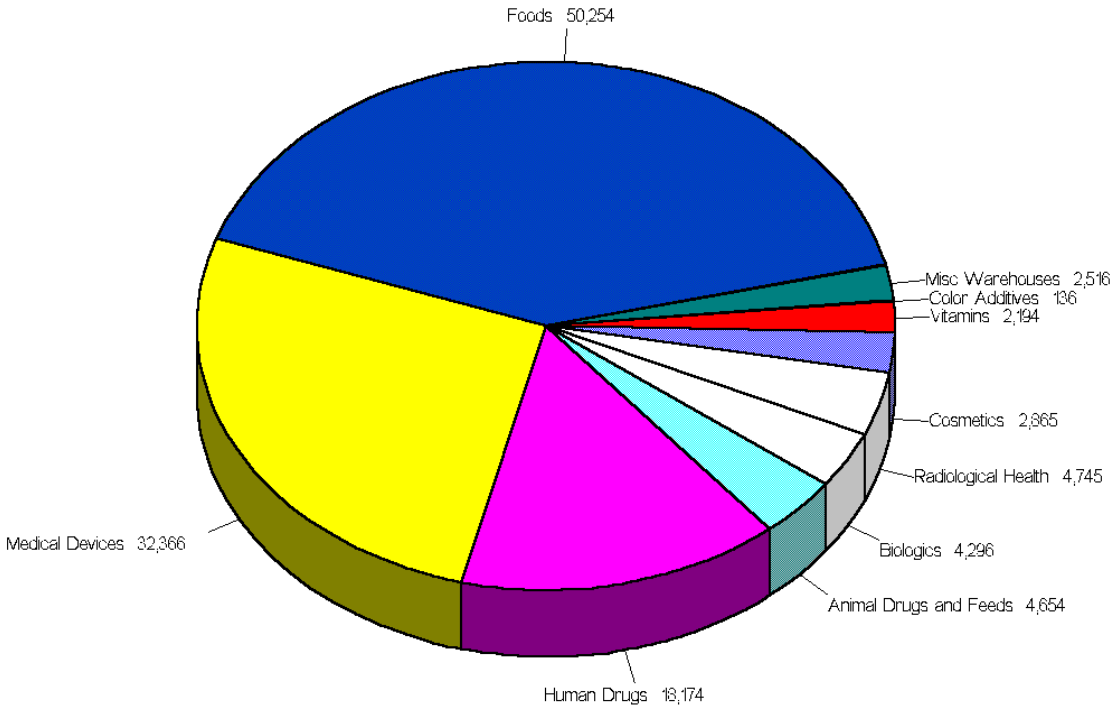
The FDA is divided into two main functional components: Headquarters, a centrally located entity, which contains the chief regulating officials who set directives on how the laws administered by the Agency will be enforced, and Field Offices, a number of entities located throughout the U.S., which contain the operational personnel who follow the directives issued by Headquarters. The Field Offices, often referred to as "the eyes and ears" of the FDA are facilities which house the FDA inspectional and laboratory operations. Approximately half of the FDA's 9,000 employees are assigned to field offices. ORO governs the activities of these Field Offices.

The number, type and size of the field offices within an area of the U.S. will vary dependent upon the population density and number of FDA regulated firms within the area. As indicated on the appended chart, the U.S. is divided into five regional areas. There are three types of Field Offices: Regional, District, and Resident Posts. Each regional area contains a Regional Office, which oversees the operation of District Offices located in the major cities of many States within the region. The size and composition of the District Office will vary dependent upon the "workload" within the city or area of their jurisdiction, for example, in major population Areas such as New York City, NY; Los Angeles, CA; and Chicago, IL, the District Office will contain a sizable inspectional force and a laboratory. Areas with a very low population density or a lack of FDA regulated firms such as Fargo, ND, will contain only the smaller Resident Posts.

Each District Office has an "inventory" of FDA regulated firms which are periodically visited and an establishment inspection is performed to determine the status of the firm's compliance with laws administered by FDA. The Investigations Branch within the District is charged with visiting firms to perform inspections, the collection of samples for monitoring the status of products (including foods, drugs, cosmetics, biologics, radiation-emitting products and medical devices), and conducting investigations to obtain information upon direction of Headquarters. Inspection of firms for compliance with the Quality Systems (QS) regulation are initiated in this manner. District Offices in cities which are international ports of entry for imported products have dedicated Import Branches which monitor these activities. Headquarters issues Import Alerts to Field Offices which contain a listing of products that may be detained without physical examination upon entry. Products are placed upon Import Alert when evidence reveals the product to be adulterated or misbranded. Additionally, the Import Branch has the discretion to decided which products will be sampled and which will be released without examination. District Office import activities are coordinated between the numerous Field Offices by the Division of Import Operations and Policy (DIOP) which is located within ORO. In this manner, ORO can coordinate activities throughout the United States to ensure that each District is following the same set of guidelines and that regulatory actions are being uniformly applied. It also serves to immediately alert every District Offices of potential problem areas being encountered in other areas of the country.

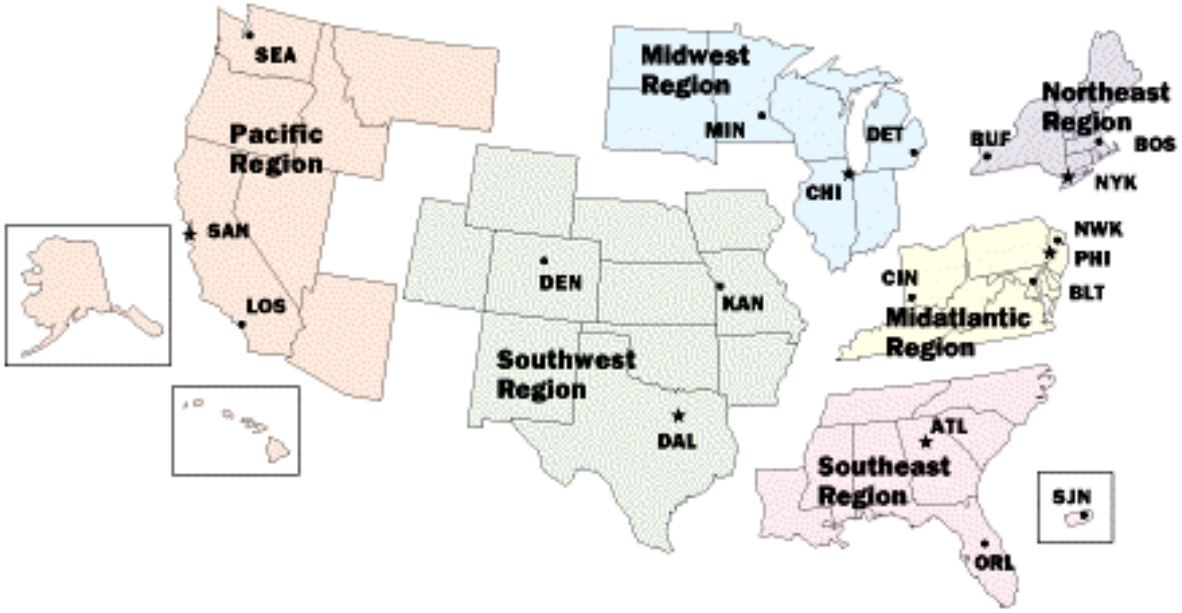
FDA Inspection Responsibilities

Total Establishments* 113,170



*FDA defines establishments as a business or other facility under one ownership and at one geographic location or address that processes, manufacturers, labels, repacks, stores, distributes, tests, or otherwise manipulates products under the jurisdiction of FDA. In addition, certain individuals or goups of individuals whose activities fall under the jurisdiction of FDA are also establishments. The sum of all categories is greater than the total because some establishments do business in more than one category.

FDA Field Sites



*The Midwest and Midatlantic Regions have been merged into a new "Central Region".

FDA REGULATORY ACTIONS APPLICABLE TO MEDICAL DEVICES

The following administrative actions or sanctions may be applied by FDA to U.S. and foreign devices distributed within the U.S., their manufacturers, importers and distributors, and may also be applied to devices exported from the U.S. and their distributors, when the devices are discovered to be in violation of the Federal Food Drug & Cosmetic (FFD&C) Act.

- **FDA-Initiated or Voluntary Recall** - Recalls are procedures by which a hazardous or potentially hazardous product is removed from the marketplace, or if additional information needed for the safe use of the product is conveyed to the user. Recalls can be initiated by either FDA or the manufacturer. FDA's Office of International Affairs notifies foreign countries of all recalls involving products exported from the U.S.; however, foreign governments are under no obligation to permit return of recalled products.

- **Warning Letter** - Correspondence is sent to a firm indicating FDA may seek more severe sanctions if the violations described are not corrected. Warning letters are issued to bring about prompt correction of violations that pose a hazard to health or that involve economic deception, before pursuing more severe sanctions, mentioned below.

- **Citation** - Formal warning to a firm of FDA's intention to prosecute the firm if violations of the law are not corrected. It provides the firm an opportunity to convince FDA not to prosecute.

- **Prosecution** - A criminal action filed by FDA against a company or individual charging violation of the law for past practices.

- **Seizure** - A civil court action against a specific quantity of goods whereby FDA seeks to remove these goods from commercial channels. After seizure, no one may tamper with the goods except by permission of the court. The owner or claimant of the seized merchandise is usually given approximately 30 days by the court to decide on a course of action. If no action is taken, the court will recommend disposal of the goods. If the owner decides to contest the government's charges, the case will be scheduled for trial. A third option allows the owner of the goods to request permission of the court to bring the goods into compliance with the law. The owner of the goods is required to provide a bond (money deposit) to assure that the orders of the court will be performed, and the owner must pay for FDA supervision of any activities by the company to bring the goods into compliance.

- **Civil Money Penalties** - Section 303(f) of the FFD&C Act, authorizes FDA, after an appropriate hearing, to impose civil money penalties for violations of the law which relate to medical devices. It is expected that these penalties may be sought in addition to other available remedies of recall, injunction, seizure, or prosecution. In determining the amount of civil penalty, FDA will take into account the nature, circumstances, extent, and gravity of the violations, the violator's ability to pay, the effect on the violator's ability to continue to do business, and any history of prior violations. The civil penalty may not exceed $15,000 for each violation and may not exceed $1,000,000 for all violations adjudicated in a single proceeding, per person.

FDA Public Advisory Committees

FDA enlists the aid and expertise of outstanding private sector scientists across the country to help the agency reach decisions, particularly concerning controversial issues or new and unusual products.

Office of the Commissioner

Science Board to the FDA

Center for Biologics Evaluation and Research

Allergic Products Advisory Committee
Biological Response Modifiers Advisory Committee
Blood Products Advisory Committee
Vaccines and Related Biological Products Advisory Committee

Center for Drug Evaluation and Research

Anesthetic and Life Support Drugs Advisory Committee
Anti-Infective Drugs Advisory Committee
Antiviral Drugs Advisory Committee
Cardiovascular and Renal Drugs Advisory Committee
Dermatologic Drugs Advisory Committee
Drug Abuse Advisory Committee
Endocrinologic and Metabolic Drugs Advisory Committee
Fertility and Maternal Health Drugs Advisory Committee
Gastrointestinal Drugs Advisory Committee
Generic Drugs Advisory Committee
Medical Imaging Drugs Advisory Committee
Nonprescription Drugs Advisory Committee
Oncologic Drugs Advisory Committee
Peripheral and Central Nervous System Drugs Advisory Committee
Psychopharmacologic Drugs Advisory Committee
Pulmonary-Allergy Drugs Advisory Committee

Center for Food Safety and Applied Nutrition

Food Advisory Committee

Center for Devices and Radiological Health

Device Good Manufacturing Practices Advisory Committee
Medical Devices Advisory Committees
Anesthesiology and Respiratory Therapy Devices Panel
Circulatory System Devices Panel
Clinical Chemistry and Clinical Toxicology Devices Panel
Dental Products Panel
Ear, Nose, and Throat Devices Panel
Gastroenterology and Urology Devices Panel
General and Plastic Surgery Devices Panel

General Hospital and Personal Use Devices Panel
Hematology and Pathology Devices Panel
Immunology Devices Panel
Microbiology Devices Panel
Neurological Devices Panel
Obstetrics and Gynecology Devices Panel
Ophthalmic Devices Panel
Orthopedic and Rehabilitation Devices Panel
Radiological Devices Panel
National mammography Quality Assurance Advisory Committee
Technical Electronic Product Radiation Safety Standards Committee

Center for Veterinary Medicine

Veterinary Medicine Advisory Committee

National Center for Toxicological Research

Ranch Hand Advisory Committee
Science Advisory Board

Other Federal Agencies with FDA-Related Duties

U.S. Department of Agriculture
- meat and poultry
- animal vaccines
- grain inspection

FAX (202) 720-2166

Consumer Product Safety Commission
- consumer products such as household appliances (except those that emit radiation), baby furniture and toys
- child-resistant packages

FAX (301) 504-0127

Environmental Protection Agency
- pesticides (sets tolerance levels for residues on feed crops and raw and processed foods)
- municipal water supplies

FAX (703) 308-4776

Bureau of Alcohol, Tobacco, and Firearms
- alcoholic beverages and tobacco

FAX (202) 927-7862

Drug Enforcement Administration
- drugs of abuse

FAX (202) 307-9765

U.S. Department of Commerce
- exports

FAX (202) 482-5270

Health Care Financing Administration (HCFA)
- health care subsidies

FAX (410) 786-4633

Federal Trade Commission
- nonprescription drug and cosmetic advertising

FAX (202) 326-2050

National Marine Fisheries Services
- voluntary seafood inspection program

FAX (301) 713-2258

Occupational Health and Safety Administration
- workplace safety standards

FAX (202) 219-4761

U.S. Customs Service
- imports

FAX (410) 962-7470

Federal Bureau of Investigation
- Federal Anti-Tampering Act

FAX (202) 324-4705

Centers for Disease Control and Prevention
- Epidemiology of diseases and other health problems

FAX (404) 488-5973

Nuclear Regulatory Commission
- Licensing and regulation of the nuclear industry

FAX (301) 415-7020

THE FDA MODERNIZATION ACT OF 1997

The FDA Modernization Act of 1997 is a major legislation focused on reforming the regulation of food, medical products, and cosmetics. The following are the most important provisions of the act:

Prescription Drug User Fees
The act reauthorizes, for five more years, the Prescription Drug User Fee Act of 1992 (PDUFA). In the past five years, the program has enabled the agency to reduce to 15 months the 30-month average time that used to be required for a drug review before PDUFA. This accomplishment was made possible by FDA managerial reforms and the addition of 696 employees to the agency's drugs and biologics program, which was financed by $329 million in user fees from the pharmaceutical industry.

FDA Initiatives and Programs
The law enacts many FDA initiatives undertaken in recent years under Vice President Al Gore's Reinventing Government program. The codified initiatives include measures to modernize the regulation of biological products by bringing them in harmony with the regulations for drugs and eliminating the need for establishment license application; eliminate the batch certification and monograph requirements for insulin and antibiotics; streamline the approval processes for drug and biological manufacturing changes; and reduce the need for environmental assessment as part of a product application.

The act also codifies FDA's regulations and practice to increase patient access to experimental drugs and medical devices and to accelerate review of important new medications. In addition, the law provides for an expanded database on clinical trials which will be accessible by patients. With the sponsor's consent, the results of such clinical trials will be included in the database. Under a separate provision, patients will receive advance notice when manufacturer plans to discontinue a drug on which they depend for life support or sustenance, or for a treatment of a serious or debilitating disease or condition.

Information on Off-Label Use and Drug Economics
The law abolishes the long-standing prohibition on dissemination by manufacturers of information about unapproved uses of drugs and medical devices. The act allows a firm to disseminate peer-reviewed journal articles and reference texts about an off-label indication of its product, provided the company commits itself to file, within a specified time frame, a supplemental application based on appropriate research to establish the safety and effectiveness of the unapproved use or obtains an exemption from the supplemental application requirement. Dissemination is limited to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and Federal and State government agencies.

Pharmacy Compounding
The act creates a special exemption to ensure continued availability of compounded drug products prepared by pharmacists to provide patients with individualized therapies not available commercially. The law, however, seeks to prevent manufacturing under the guise of compounding by establishing parameters within which the practice is appropriate and lawful.

Risk-Based Regulation of Medical Devices
The act complements and builds on FDA's recent measures to focus its resources on medical devices that present the greatest risks to patients. For example, the law exempts from premarket notification class I devices that are not intended for a use that is of substantial importance in preventing impairment of human health, or that do not present a potential unreasonable risk of illness or injury. The law also directs FDA to focus its postmarket surveillance on higher risk devices, and allows the agency to implement a reporting system that concentrates on a respective sample of user facilities -- such as hospitals and nursing homes -- that experience deaths and serious illnesses or injuries linked with the use of devices.

Finally, the law expands an ongoing pilot program under which FDA accredits outside -- so-called "third party" -- experts to conduct the initial review of all class I and low-to-intermediate risk class II devices. The act, however, specifies that an accredited person may not review devices that are permanently implantable, life-supporting, life-sustaining, or for which clinical data are required.

Food Safety and Labeling
The act eliminates the requirement of FDA's premarket approval for most packaging and other substances that come in contact with food and may migrate into it. Instead, the law establishes a process whereby the manufacturer can notify the agency about its intent to use certain food contact substances and, unless FDA objects within 120 days, may proceed with the marketing of the new product. Implementation of the notification process is contingent on additional appropriations to cover its cost to the agency. The act also expands procedures under which FDA can authorize health claims and nutrient content claims without reducing the statutory standard.

Standards for Medical Products
While the act reduces or simplifies many regulatory obligations of manufacturers, it does not lower the standards by which medical products are introduced into the market place. In the area of drugs, the law codifies the agency's current practice of allowing in certain circumstances one clinical investigation as the basis for product approval. The act, however, does preserve the presumption that, as a general rule, two adequate and well-controlled studies are needed to prove the product's safety and effectiveness.

In the area of medical devices, the act specifies that FDA may keep products off the market whose manufacturing processes are so deficient that they could present a serious health hazard. The law also gives the agency authority to take appropriate action if the technology of a device suggests that it is likely to be used for a potentially harmful unlabeled use.

GLOBAL HARMONIZATION TASK FORCE

INTRODUCTION

The Global harmonization Task Force (GHTF), an international forum focused on medical devices regulation, has embarked on a number of regulatory initiatives designed to move the participating countries closer to achieving the goal or mutual recognition of regulatory processes.

SCIENCE/FACTS

Formed in 1992, the GHTF is comprised of government and industry representatives from North America, Europe and Asia/Australia, as well as observers from South Korea, China, Brazil, Argentina and Poland, WHO, CEN and ISO. The GHTF is structured to have one main task force which meets once a year. In addition to the main task force, four study groups were formed to concentrate on a particular aspect of medical device regulation. These groups meet three or four times a year.

Initially, the objectives of the main task force were primarily focused on aligning quality system requirements in order to build upon previous international efforts in this area. These significant collective efforts resulted in the harmonization of quality system requirements in the U.S., Canada, Japan and the EU as well as the development of a guidance document on the achievement of the task force. Based on the success of these projects, the GHTF has committed to undertake new assignments within the four study groups.

The meetings of the main task force of the GHTF have been held in Nice in 1992, Tokyo in 1993, Vancouver in 1995, Lisbon in 1996 and in Sidney in 1998.

FDA POSITION

FDA is committed to full participation in the advancement of the GHTF's mission and initiatives. During the past year, FDA has been actively involved in GHTF projects and significant progress has been made.

- During the June 1995 main task force meeting in Vancouver, Canada, FDA recommended that (1) a new study group be established on adverse event reporting and (2) that the GHTF examine ways of harmonizing premarket approval packages. The task force accepted both recommendations - FDA agreed to provide the convener for the new study group (Study Group 2) and Study Group 1 agreed to accept the task on developing a universal format for premarket submission packages.

- Study Group 1 (regulatory systems) has made significant progress in the development of a premarket package. The committee agreed on the selection of three devices for the initial review. FDA then proposed and developed a notebook format which would reference each country's requirements in an index. With input from the study group members, all requirements for each country will be included in one notebook for each product.

As these notebooks are compiled, the Study Group will examine areas where the requirements can be harmonized.

In 1997, Study Group 1's work continued with one meeting held to present initial suggest submission formats to EU notified bodies as well as FDA.

- During the first meeting of Study Group 2 (post-market vigilance), the members shared information on the adverse event reporting systems in their countries, developed the charge for the group and identified tasks that would allow the group to accomplish the goals of sharing information. These tasks, which are being handled by subgroups, are:

  (1) harmonize language,
  (2) develop examples of situations to facilitate interpretation,
  (3) establish guidelines for reporting to users (to authorities and to manufacturers),
  (4) consider what to say and how to inform the public about reports, and
  (5) provide liaison to coordinate activities.

  The Study Group took up the issue of electronic data interchange (EDI) in 1997, to develop definitions for terms used in each of the documents and to consider whether to expand the focus to include manufactures reporting of information concerning events to health professionals and device users in general.

- Study Group 3 (quality systems). After achieving success in the harmonization of a quality systems standard, this group took up a guidance document relating to quality control validation.

- Study Group 4 (auditing). This group prepared a GHTF guidance document on regulatory auditing of quality systems of medical device manufacturers.

A general set of issues has arisen about publication of final guidance documents, their global availability, and their enforceability. Although no decisions were made, there appeared to be a general consensus on:

- the need for a mechanism to disseminate the materials to national health authorities, either via the World Wide Web and/or in hard copy form;
- the necessity for periodic updating to ensure the material in the documents remains fresh, relevant and usable; and
- the possibility of making the documents administratively enforceable, which would require "credentialing" by the full GHTF.

  ISO's TC-210 committee is addressing four areas:

- documentation on quality systems, which will consist of technical procedures for implementing the ISO-9000 standards series relating to quality systems for medical devices (publication is anticipated next year) followed a year later by a formal standard;

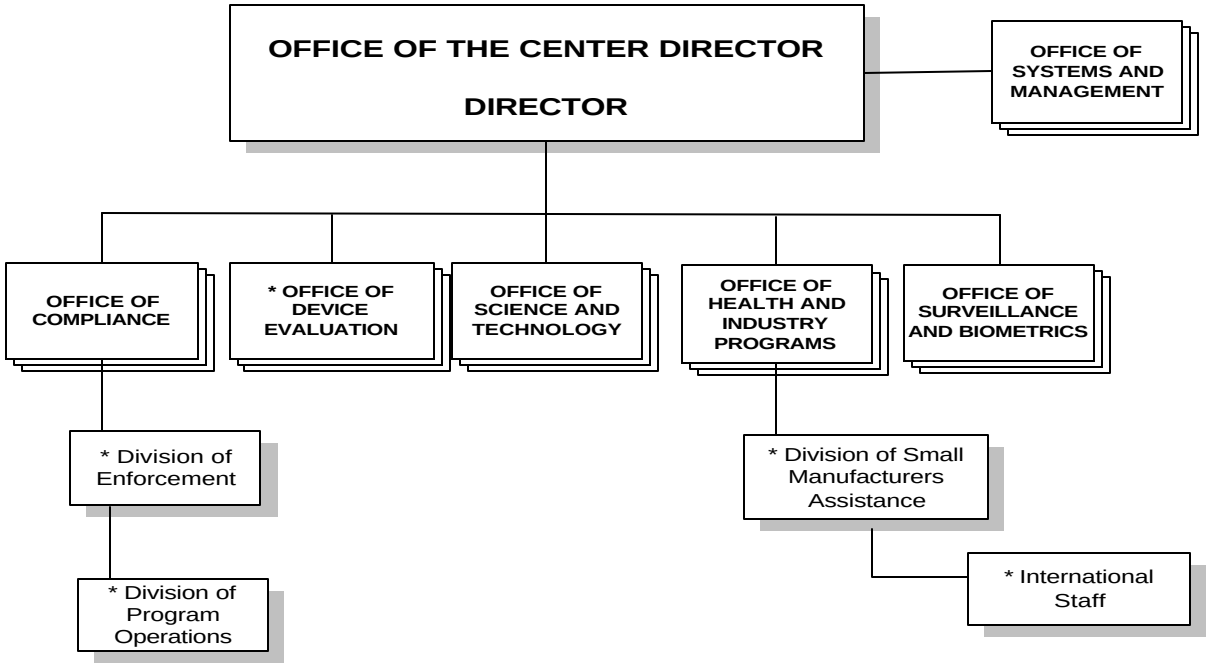
- guidance for countries pursuing regulations on quality systems regarding the process for drafting the rules so as to promote coherent standards from nation to nation;
- organizing symbols, nomenclature and labeling requirements to better assure uniformity among nations; and
- a joint ISO/IEC venture aimed at producing guidance on how to conduct risk analysis and risk management programs.

PART II.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

STRUCTURE AND FUNCTIONS

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH



* Offices that primarily deal with international issues

Please note: The initial point of contact for Government to Government requests involving medical devices should be the International Relations Staff (address on the front cover)

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

FUNCTIONS

Develops and carries out a national program to assure the safety, effectiveness, and truthful labeling of medical devices for human use.

Reviews and evaluates medical device premarket approval (PMA) applications, product development protocols (PDPs), exemption requests for investigational devices (IDEs), and premarket notifications [510(k)s].

Plans, conducts, and supports research and testing to provide the scientific and technological base required for risk assessment, evaluation, compliance, and performance standards development relating to medical devices and radiation-emitting electronic products.

Collects information about injuries and other adverse experience in the use of medical devices and radiation-emitting electronic products and uses this information when planning Center activities.

Develops, promulgates, and enforces performance standards for medical devices and radiation-emitting electronic products, and quality system requirements, formally good manufacturing practices (GMP's).

Develops, direct, evaluations, and monitors compliance and surveillance programs for medical devices and radiation-emitting electronic products.

Provides technical and other nonfinancial assistance to small manufacturers of medical devices.

Develops and carries out a national program designed to control unnecessary exposures of humans to ionizing and nonionizing radiation-emitting electronic products and assure its safe and efficacious use.

Develops and implements training and educational programs relating to radiological health and medical device issues for other Federal, State, and local agencies, the professional community, consumers, and the public.

Enters into agreements with foreign countries regarding the regulation of devices to facilitate commerce in medical devices between the U.S. and other countries.

CDRH's OFFICE OF DEVICE EVALUATION (ODE)

Plans, conducts, and coordinates appropriate Center actions regarding approval, denial, and withdrawal of approval of premarket approval (PMA) applications, product development protocols (PDP's) and investigational device exemptions (IDE's), and makes substantial equivalent determinations for 510(k)'s, and monitors sponsors' conformance with requirements of all programs.

Conducts a continuing review, surveillance, and medical evaluation of the labeling, clinical experience, and required reports submitted by sponsors.

Provides support to medical device advisory panels; recommends establishing or restructuring such panels as appropriate.

Develops and interprets regulations and guidelines regarding device classification, IDE's, PMA's, PDP's and 510(k)'s.

Coordinates Center device classification activities; reviews petitions for or initiates reclassification of medical devices.

Participates in the development of national and international consensus standards, and voluntary guidelines, through interaction with appropriate national and international standards committees.

CDRH's OFFICE OF SURVEILLANCE AND BIOMETRICS

Advises, coordinates, and provides consultation to the Center Director and other Agency officials including the commissioner on Center programs and policies concerning premarket review activities, postmarket management activities, surveillance and biometrics programs and activities, and regulatory matters for medical devices and radiological products.

Establishes policy for surveillance programs. Designs, develops, and implements a Center program to acquire device experience information; identifies and analyzes device problems; develops solution strategies to such problems; and tracks programs or solution implementations.

Provides statistical, epidemiological, and biometric services, and conducts research in support of the operating and scientific programs of the Center.

Represents the Center with other governmental agencies (Federal, State, and International), industry, and consumer organizations on issues related to the activities of the Office including postmarket management activities.

Provides consultation to Center Offices on health economics and cost effectiveness methodology issues pertaining to claims for medical devices.

Plans, develops, and implements office administrative support and services including program planning, financial management, extramural and collaborative efforts, procurement, travel, personnel administration, employee development and training, employee evaluations, recognition programs, property management, and facility management.

CDRH's OFFICE OF COMPLIANCE (OC)

Advises the Center Director and other agency officials on legal, administrative, and regulatory programs and policies concerning agency compliance responsibilities relating to medical device and radiological health activities.

Develops, directs, coordinates, evaluates, and monitors compliance and surveillance programs covering regulated industry.

Conducts field tests and inspections when necessary for regulatory purposes and evaluates industry quality control and testing programs to assure compliance with regulations.

Provides advice to agency field offices on, and manages Center activities relating to, regulations, case development, and cases where findings are challenged.

Designs, develops, and implements Center programs to register device establishments and list products with FDA.

Manages and coordinates Center activities under the Compliance Status (COMSTAT) and Bioresearch Monitoring Programs.

Coordinates all field planning activities and issues all field assignments for the Center. Provides technical support and guidance in the development and review of standards and regulations, and the training of Federal and State compliance personnel.

Advises actual or potential manufacturers concerning the requirements of the law and regulations.

CDRH's OFFICE OF HEALTH AND INDUSTRY PROGRAMS (OHIP)

Analyzes medical device and radiation-emitting product user-related problems and conducts research, applying systems analysis and human factors to problem identification and solution strategies. Implements and evaluates these strategies.

Conducts and evaluates programs to provide technical and other non-financial assistance to small manufacturers of medical devices to promote their understanding of compliance with the medical device amendments and regulations.

Provides, maintains, and applies expertise in communications technology in support of Center and FDA programs.

Drafts regulations for publication in the Federal Register.

Develops and implements strategies for obtaining, analyzing, and incorporating the views and needs of health professionals, lay device users, and industry into the Center policy and decisions-making processes as well as in the problem analysis, resolution strategy development, implementation, and evaluation processes.

Operates a program to implement the Mammography Quality Standards Act of 1992.

Supports a Staff College used to train employees and make available technology updates to CDRH staff.

DIVISION OF SMALL MANUFACTURERS ASSISTANCE (DSMA)

Directs a program to provide technical and other non-financial assistance to small manufacturers of medical devices and radiation-emitting products to promote understanding of and compliance with applicable laws and regulations.

Serves as a central coordinating point to assist small manufacturers of medical devices and radiation-emitting products in contacting appropriate agency and Center components, as well as other Federal and State agencies.

Serves as a central coordinating point to assist manufacturers in obtaining information about the status of their premarket applications.

Identifies program information needs of small manufacturers of medical devices and radiation-emitting products, and develops and conducts communication and education programs for them in conjunction with other agency components. Suggests changes to ameliorate unexpected adverse effects.

Presents and explains relevant Center activities, plans, policies, and decisions to small manufacturers and their trade and professional associations.

INTERNATIONAL STAFF

Coordinates the development of agreements with foreign countries, in conjunction with appropriate agency officials, to facilitate commerce of medical devices between the U.S. and such countries consistent with the requirements of the Federal Food, Drug, and Cosmetic (FFD&C) Act.

Encourages the mutual recognition of the quality systems regulation (QSR) [good manufacturing practices (GMP's)] in accordance with the applicable sections (i.e. 519, 520(f) etc.) of the FFD&C Act and other regulations and testing protocols as determined to be appropriate.

Identifies and establishes priorities for international harmonization of regulatory requirements for medical devices.

Monitors international regulatory initiatives that impact on the U.S. medical device program.

Establishes and maintains dialogue with foreign governments and international government organizations, to include coordination of meetings with these countries, coordination of U.S. technical assistance programs and international notification of significant health risks associated with medical devices.

Participates with other U.S. government agencies (e.g., Department of Commerce, United States Trade Representative, and the Department of State) in interagency discussions, in trade negotiations and other trade related discussions leading to implementation of trade agreements with other countries.

Establishes, implements, and maintains the International Reference System for the Center. This involves establishing and maintaining a reference library that supports CDRH international activities. It consists of medical device requirements of foreign countries, national/international standards, international publications and conference proceedings.

Directs and coordinates visits by international officials to the Center and brief them on matters of mutual concern in the area of medical devices.

PART III.

FDA'S REGULATION

OF

MEDICAL DEVICES

IMPORTATION OF MEDICAL DEVICES

Foreign firms that manufacture medical devices sold in the United States and U.S. distributors ("importers") of medical devices must comply with applicable U.S. laws before, during, and after importing a medical device into the U.S. or its territories.

The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act define a medical device in Section 201(h) as **"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including any component, part, or accessory, which is:**

- **Recognized by the official National Formulary, or the United States Pharmacopoeia (USP), or any supplement to them.**

- **Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation treatment, or prevention of disease, in a man or other animals.**

    - **Intended to affect the structure or any function of the body of a man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of a man or other animals and which is not dependent upon being metabolized for the achievement of its principal intended uses."**

Foreign establishments engaged in the manufacture, preparation, propagation, compounding, or processing of a device that is imported, or offered for import, into the U.S. must register their establishments and provide the FDA with the name of the U.S. agent representing their establishment. Foreign establishments must also continue to file device listing forms for medical devices they are exporting to the U.S. FDA is also authorized to enter into cooperative agreements with foreign countries to ensure that non-compliant products are refused entry into the U.S.

The importation of medical devices into the U.S. is subject to the laws of the FFD&C Act. They are:

- Sections 481-521 of the Tariff Act (TA) of 1930, as amended (19 U.S.C. 1521), enforced by the U.S. Customs Service of the Department of Treasury which sets the entry requirements for all imports into the U.S.

- Section 510(I) and (k) Registration of Procedures for Drugs and Devices

- Section 519 Records and Reports on Devices

- Section 801(a), (b), and (c) of the Federal Food, Drug, and Cosmetic (FFD&C) Act (21 U.S.C. 381 (a), (b), and (c)) which contains special requirements for the import of medical devices and section 536 which contains special requirements for the import of radiation-emitting electronic products.

- Section 801(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 381 (d)) which permits the importation of medical device component parts or accessories or other articles of devices so long as the imported item is further processed or incorporated into a product that will be exported. If the imported item is not exported, it must be destroyed.

WORKING AGREEMENT BETWEEN FDA AND U.S. CUSTOMS SERVICE

Section 481-521

The major responsibility of the U.S. Customs Service is to administer the Tariff Act of 1930 as amended. Primary duties include assessment and collection of all duties, taxes, and fees on imported merchandise; administration and review of import entry forms; the enforcement of U.S. Customs and related laws; and administration of certain navigation laws and treaties. Currently, there is a working agreement between FDA and U.S. Customs for the cooperative enforcement of Section 801 of the FFD&C Act. Most cooperative action centers on violations of the FFD&C Act, particularly noncompliance with FDA import requirements, or when FDA determines it necessary to sample imported devices to assure their safety and effectiveness.

The first process, as shown on the following "Import Procedures Flowchart," includes the importer or filer submitting the necessary entry information to the local U.S. Customs district office. For those entries not filed electronically, a paper entry consisting of the commercial invoice, Customs entry forms CF3461/3461ALT and/or CF7501 or documentation that would need to be provided by the importer or filer. Most importers ask that domestic customhouse brokers complete these forms and make the submissions on their behalf. However, this does not always result in the immediate release into U.S. commercial channels. Furthermore, submitting these forms does not release the importer from responsibility to assure FDA that the premarketing or other requirements have been met. When an entry is filed with U.S. Customs, a copy of the entry is also provided to the local FDA district office.

Section 510(I) and (k) Registration of Procedures of Drugs and Devices

The FDA district office then determines if the product complies with FDA requirements. For devices intended for commercial distribution in the U.S., this includes assuring that the importer or original distributor is registered, the foreign manufacturer has registered and listed their establishments and devices and provided FDA with the name of the U.S. agent representing their establishment, that the device is compliant with the Quality Systems (QS) regulation and is properly labeled. The device has been given clearance or approval for marketing following the submission of a 510(k) premarket notification [or is exempt] of a PMA. If the FDA district office determines that the device, manufacturer, or importer has not complied with FDA import requirements, the device will be detained at the port of entry and the importer will be given a "Notice of Detention and Hearing." At this point, the importer, the foreign manufacturer, or the device itself must be brought into compliance before the device is released.

Section 801

FDA may examine certain devices to assure their safety and effectiveness. When this occurs, FDA will issue a "Notice" to the "importer of a record," who may or may not be the initial distributor on a form titled "Notice of FDA Action." Sampling may involve examining the product at the port of entry or physical collection of a statistical portion of the lot for analysis by an FDA laboratory.

If there is a problem, or if the sample is determined to be out of compliance with required specifications, the device will be detained and the "importer of record" will be issued a "Notice of FDA Action" indicating that the article is being detained due to the appearance of a violation under the FFD&C Act. Under certain conditions, the "importer of record" of a device that has been detained, is given an opportunity to submit application for authorization to bring the device into compliance with the Act. If FDA permits reconditioning, another sample may be collected and analyzed after reconditioning. If the device is then determined to be in compliance, it will be released. If the "importer of record" fails to properly recondition the device, or FDA does not permit reconditioning, the "importer of record" must either export or destroy that particular lot. Failure to do so within 90-days may result in issuance of a Customs Redelivery Notice and an assessment for liquidated damages for up to 3 times the value of the lot.

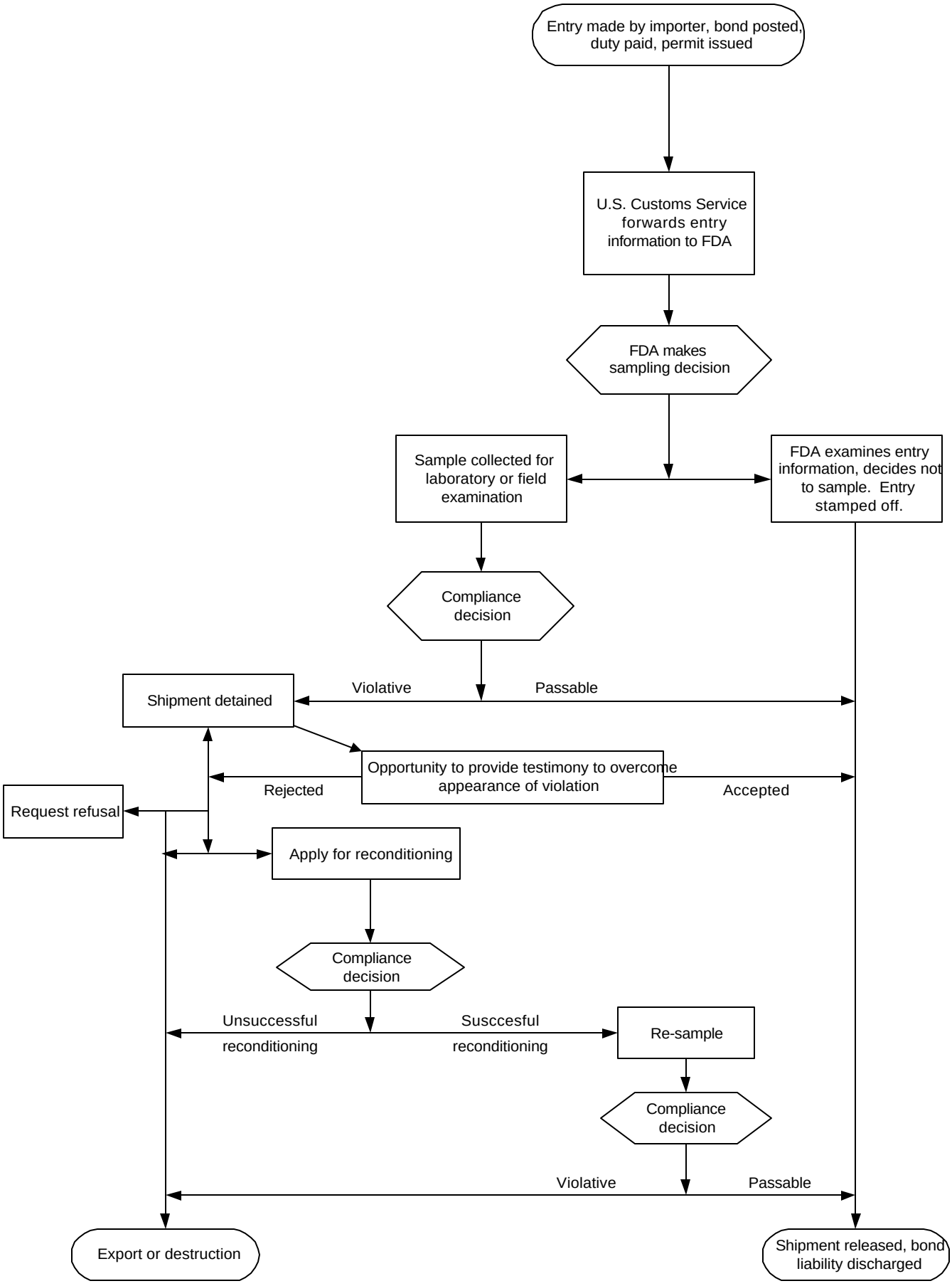
Section 519

Operational and Administrative Systems for Import Support (OASIS)

The FDA computerized import system, known as the Operational and Administrative System for Import Support (OASIS), became fully operational in all district offices in November 1997 to expedite and support a "paperless" import of goods into the U.S. The OASIS program is an electronic interface between FDA and the Customs Service's Automated Commercial System (ACS). OASIS is an on-line interactive and automated system, which replaced the existing process of reviewing the paperwork for import entries manually. This computer-generated system supports FDA's ability to effectively regulate imported products. Through the use of OASIS, FDA is focusing on high risk, suspect, or known problem products while allowing the lower risk products into domestic commerce more efficiently. This system will expedite the flow of international commerce and the needs of the importing community.

OASIS enables Customhouse filers to transmit their entry data to FA electronically at the same time they are transmitting their required electronic data to the U.S. Customs Service. Within 15 minutes of keying in the data, the filer receives a computerized response stating whether the entry requires further FDA review, or if it can move immediately into domestic commerce.

Import Procedures Flowchart



U.S. CLASSIFICATION OF MEDICAL DEVICES

Medical devices vary widely in their complexity and their degree of risk or benefits. They do not all need the same degree of regulation. Thus, U.S. FDA places all medical devices into one of three regulatory classes based on the level of control necessary to assure safety and effectiveness of the device.

These classes are:

Class I = General Controls
Class II = General Controls and Special Controls
Class III = General Controls and Premarket Approval

The class of most devices can be found in the classification regulations in Title 21 Code of Federal Regulations (CFR) Parts 862 through 892. There are approximately 1,700 device classifications within 16 medical specialties. Of the 1,700 classified devices, 45% are Class I, 47% are Class II and 8% are Class III.

CLASS I - GENERAL CONTROLS

Class I devices are subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject to "General Controls" as are Class II and Class III devices.

General controls include:

1. Establishment registration (use FDA Form 2891) of companies which are required to register under 21 CFR part 807.20, such as manufacturers, distributors, repackagers and relabelers, and foreign firms.
2. Medical device listing (use FDA Form 2892) with FDA of devices to be marketed.
3. Manufacturing devices in accordance with the Quality Systems regulation (GMP's) in 21 CFR Part 820.
4. Labeling devices in accordance with labeling regulations in 21 CFR Part 801 or 809.
5. Submission of a premarket notification 510(k) before marketing a device.

Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Most Class I devices are exempt from the premarket notification and/or the Quality System regulation. These exemptions are listed in attachment A.

CLASS II - SPECIAL CONTROLS

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls.

Special controls may include special labeling requirements, mandatory and voluntary performance standards and postmarket surveillance.

Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes. Class II devices are usually not exempt from the premarket notification or the Quality System regulation.

CLASS III - PREMARKET APPROVAL

Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls.

Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

Premarket approval is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Not all Class III devices require an approved premarket approval application for marketing. Class III devices which are equivalent to devices legally marketed before May 28, 1976 may be marketed through the premarket notification [510(k)] process until FDA has published a requirement for manufacturers of that device type to submit premarket approval data.

Class III devices which require an approved premarket approval application to be marketed are those:

1. Regulated as new devices prior to May 28, 1976, also called transitional devices.
2. Devices found not substantially equivalent to devices marketed prior to May 28, 1976.
3. Class III preamendment devices, which by regulation in 21 CFR, require a premarket approval application.

Class III devices which can be marketed with a premarket notification 510(k) are those:

1. Postamendment (i.e. introduced to the U.S. market after May 28, 1976) Class III devices which are substantially equivalent to preamendment (i.e. introduced into the U.S. market before May 28, 1976) Class III devices and for which the regulation calling for the premarket approval application has not been published in the CFR.

SECTIONS RELATED TO DEVICE CLASSIFICATION

Note: Section 206 and 207 include provisions for the classification of Class II and Class III devices. Section 206 contains requirements that exempt certain Class I and II devices from Premarket Notification. Section 207 contains a requirement that allows for classification of new, low risk, Class III devices. These provisions are addressed in the Premarket Notification (Section 206) and Premarket Approval (Section 207) of the FFD&C Act.

Section 416 - Product Classification (Combination Products)

Any person who submits an application or submission for a product may recommend to FDA a classification for the product or the component of FDA the applicant believes to be most appropriate to regulate the product. The request can recommend classifying the product as a drug, biological product, device, or a combination product under Section 503(g) of the FFD&C Act.

Not later than 60 days after receipt of the request, FDA must determine the classification or the component that will regulate the product, and must provide a written statement to the requester that identifies the classification or component and the reasons for the determination. The written statement cannot be changed without consent of the requester or for public health reasons based on a scientific evidence. If FDA does not respond with 60 days, the requester's recommendation becomes the final FDA determination and cannot be changed without the written consent of the requester or for public health reasons based on scientific evidence.

Effective: February 19, 1998

CHANGES IN DEVICE CLASSIFICATION

The Act contains provisions for changing the classification of a device. Changes in classification are based on FDA's receipt of new information about a device. FDA may, on its own or in response to an outside petition, change a device's classification by regulation.

A manufacturer who wishes to have a device reclassified to a lower class, must convince FDA that the less stringent class requirements will be sufficient to provide reasonable assurance of safety and effectiveness.

Section 207 - Risk Based Classification of Postamendment Class III Devices

An applicant who submits a Premarket Notification Submission [510(k)] and receives a Not Substantially Equivalent (NSE) determination, placing the device into a Class III category, can request FDA to classify the product into Class I or II>

The request must be in writing and sent within 30 days from the receipt of the NSE determination. In addition, the request must include a description of the device, reasons for the recommended classification (into Class I or II), and information to support the recommendation. Within 60 days from the date the written request is submitted to FDA, the Agency must classify the device by written order. If FDA classifies the device into Class I or II, this device can be used as a predicate device for other 510(k)'s.

However, if FDA determines that the device will remain in Class III, the device cannot be distributed until the applicant has obtained an approved Premarket Approval (PMA) application or an approved Investigational Device Exemption (IDE).

Within 30 days of notifying the applicant of the determination that the device has been classified into Class I or Class II, FDA will announce the final classification in the Federal Register.

Effective: February 19, 1998

IMPORT REQUIREMENTS TABLE

The import requirements that foreign manufacturers and/or distributors or importers must comply with before importing a medical device into the United States are listed on the table below. In addition, each import requirement is authorized either by the Federal Food Drug and Cosmetic (FFD&C) Act or the Tariff Act. These Acts are enforced by FDA and U.S. Customs Service. Except for the requirement to mark country of origin, these are all FDA requirements. Not all requirements on the table are applicable to both the importer and the foreign manufacturer, so take care to note what applies to each or both. There are also exemptions to some of these requirements.

Applicable requirements listed in the table must be complied with before importation into the U.S., otherwise the shipment will be subject to detention at the port of entry.

	Responsible for Submitting		Receiver of Submission	
Import Requirements	**Foreign Manufacturer**	**Initial Distributor**	**FDA**	**U.S. Customs Service**
1 Before Import				
Establishment Registration (FDA 2891)	+	+	+	
Medical Device Listing (FDA 2892)	+	+	+	
Premarket Notification 510(k)	+	+	+	
Premarket Approval	+	+	+	
Good Manufacturing Practices	+	+	+	
Medical Device Reporting	+	+	+	
Performance Standards	+	+	+	
Clinical Data	+	+	+	
Radiological Products	+	+	+	
Labeling	+	+	+	
Country of Origin	+	+		+
Postmarket Surveillance/Tracking	+	+	+	

NOTES: 1. [+] Indicates person or organiztion who files/receives form, or takes indicated action.

2. Form numbers appear in parentheses. Food and Drug Administration numbers are preceded by "FDA".

ESTABLISHMENT REGISTRATION AND MEDICAL DEVICE LISTING

Section 510 of the FFD&C Act requires both domestic and foreign manufacturers to list their devices with the FDA if the devices are in commercial distribution in the U.S. Devices are listed by their classification name on form FDA 2892. The proprietary and common or usual name of the device(s) must be submitted to FDA upon request. In addition, manufacturers must maintain a historical listing file of labeling and advertisements in accordance with Title 21 Code of Federal Regulations (CFR) 807.31.

In many other countries the term "registration" means the process by which the government clears or approves a product for marketing. In the U.S., however, neither registration nor listing constitutes FDA clearance or approval for marketing or commercial distribution. Unless the device is exempt, a premarket notification submission [510(k)] or a premarket approval application (PMA) is required before commercial distribution.

PERFORMANCE/EFFECTIVENESS REQUIREMENTS

PREMARKET NOTIFICATION - 510(k)

The faster marketing process is premarket notification or 510(k). The 510(k) applicant must demonstrate to FDA that their device is substantially equivalent to a legally marketed device, that is, one that was marketed before May 28, 1976 or one that was marketed after that date that was found substantially equivalent through the 510(k) process.

A device is substantially equivalent if, in comparison to a legally marketed device it:

- has the same intended use; and
- has the same technological characteristics as the legally marketed device,

or

- has different technological characteristics, and submitted information:
  - does not raise new questions of safety and effectiveness, and
  - demonstrates that the device is as safe and as effective as the legally marketed device.

All 510(k) applications must include descriptive information, labeling, and may require performance and effectiveness testing depending upon the devices technological characteristics and risk associated with its application.

Performance and effectiveness information may include mechanical bench testing, biocompatibility testing, animal testing and clinical evaluation. Devices in contact with the human body must be biocompatible and most implanted and life-supporting devices require clinical evaluation in support of a 510(k) application.

If the device is determined by FDA to be substantially equivalent then the device may be marketed. If FDA determines the device is not substantially equivalent, the manufacturer may resubmit another 510(k) with new data, file a petition to reclassify the device, or submit a premarket approval (PMA) application.

PREMARKET APPROVAL

The most stringent marketing application required by FDA is premarket approval or PMA. The PMA application must contain sufficient information to reasonably assure FDA of the safety and effectiveness of the device. This requires valid scientific data to demonstrate that the device is safe and effective for its intended use. In most cases, this includes well-controlled clinical studies; full reports of safety and effectiveness and data regarding the manufacturing of the device. Clinical studies to support the premarket approval application must be done in accordance with the Investigational Device Exemption (IDE) regulation.

The PMA review process consists of an administrative/filing review, scientific and regulatory review, advisory committee review/recommendation, and final documentation and notification of approval. An approved Premarket Approval Application is, in effect, a private license granted to the applicant for marketing a particular device.

About 1% of the medical devices in commercial distribution have gone through the PMA process. Class III devices marketed through the 510(k) process are preamendment devices for which FDA has not yet required the premarket approval application. FDA has been receiving approximately 50 premarket approval submissions per year.

The performance and effectiveness of medical devices marketed through the 510(k) process must only be demonstrated to the extent of substantial equivalence. That is, it must be as safe and as effective as a similar device already marketed. The performance and effectiveness of devices marketed through the PMA process must demonstrate that the device is reasonably safe and effective. These devices must demonstrate, on their own merit, safety and effectiveness through valid scientific evidence.

PRODUCT DEVELOPMENT PROTOCOL

As part of its reengineering initiative, the Food and Drug Administration, Center for Devices and Radiological Health is proposing to implement the statutory authority for Product Development Protocol (PDP). Section 515 (f) of the Federal Food, Drug, and Cosmetic Act provides this alternative process to the premarket approval process (PMA) for Class III devices. This alternative process, (PDP), was not implemented during the early years of the device program because it was considered potentially complex and there was a need to focus attention on implementing the core provisions of the Medical Device Amendments of 1076 such as the IDE, PMA, 510(k), GMP, and problem reporting requirements.

A reengineering team comprised of FDA staff, industry and other non-government representatives have focused their efforts on a proposal with the following goals:

1. provide a process that will allow FDA to effectively regulate Class III products from initial development to marketing to eventual replacement by more advanced products,
2. reduce the FDA resources required to review and approve new Class III devices,
3. reduce the total time to get a new class III device to market, and
4. no reduction in the overall assurance of safety and effectiveness as compared with the PMA process. The process will be designed to facilitate use of expertise outside FDA and will provide a clear development path "road map" for products to the market.

A series of documents available on the CDRH web site to provide current status information about PDP. (For access to the CDRH web site see Part IV.)

CLINICAL DATA (<u>International and Domestic</u>)

Clinical data may be required in support of premarket notification [510(k)] submissions and in most cases in support of a premarket approval (PMA) application.
Clinical data is required in less than 10% of all 510(k) submissions. The sole purpose of clinical data in a 510(k) would be to demonstrate equivalence in performance to another device. FDA does

not intend the data, in a 510(k), to determine the device's absolute safety and effectiveness, but to validate that it is equivalent or better, in terms of its safety and effectiveness, than another device with the same intended use.

The need for performance testing depends on what is needed to demonstrate equivalence and on the complexity of the device. For example, it is likely that little or no clinical data would be needed to determine equivalence of a laparoscopic surgical instrument. In contrast, considerable data would be necessary to judge the equivalence of an implantable cardiac pacemaker.

Clinical data is, however, required in a premarket approval application. The PMA applicant must provide a cogent demonstration of the safety and effectiveness for all diagnostic and/or therapeutic medical claims for the device based on laboratory, animal and clinical data.

Regardless of the type of marketing application, the clinical data must be based on sound scientific principles to demonstrate the endpoint of substantial equivalence or safety and effectiveness. These principles consist of a proper study design, including: controls and adequate number of patients, monitoring of the study to assure protocol is followed by the investigators, and proper analysis of results.

All clinical studies performed in the U.S. in support of a 510(k) or PMA must be conducted in accordance with the Investigational Device Exemption (IDE) regulation. This required the manufacturer to obtain approval of the study before it begins, informed consent provided to each patient, and proper monitoring during the conduct of the study.

A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

- the foreign data are applicable to the United States population, medical practice, and requirements for informed consent in conformance with the Declaration of Helsinki;
- the studies have been performed by clinical investigators of recognized competence; and
- the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

Applicants who seek approval based solely on foreign data can meet with FDA officials in a "presubmission" meeting.

PRE-IDE PROCESS

In order to facilitate the initiation of clinical trials under the IDE regulation, the Food and Drug Administration (FDA) encourages sponsors to begin communicating with the ODE reviewing division prior to the submission of the original IDE application. This communication may take the form of a "Pre-IDE" meeting and/or a "Pre-IDE" submission.

PRE-IDE MEETINGS

Two types of pre-IDE meetings are possible: meetings in which FDA provides "informal guidance" and meetings where FDA provides "formal guidance" as provided for in Section 201 of the FDA Modernization Act of 1997.

"Informal Guidance" Meetings

Sponsors are encouraged to meet with the ODE reviewing division before the IDE application is submitted for review so that the reviewing division can provide any advice/guidance which can be used in the development of supporting pre-clinical data or the investigational plan for incorporation into the IDE application. These meetings may take the form of telephone conference calls, video conferences, or face-to-face discussions. Regardless of the form of the pre-IDE meeting, all meetings should be recorded by the ODE reviewing division and reported on a quarterly basis to ODE senior management. Minutes of the meeting should include the date of the meeting, the attendees, whether material was submitted prior to the meeting for discussion/review by ODE staff, a summary of the discussion, and any recommendations or guidance provided by FDA.

"Formal Guidance" Meetings

A sponsor or applicant may submit a written request for a meeting to reach an agreement with FDA regarding FDA's review of an investigational plan (including a clinical protocol). As required by the statute, this meeting should take place no later than 30 days after receipt of the request. The written request should include a detailed description of the device, a detailed description of the proposed conditions of use of the device, a proposed plan (including a clinical protocol) for determining whether there is a reasonable assurance of effectiveness, and, if available, information regarding the expected performance of the device.

If an agreement is reached between FDA and the sponsor or applicant regarding the parameters of an investigational plan (including a clinical protocol), the terms of the agreement should be put in writing and made part of the administrative record by FDA.

Detailed procedures for implementing this new requirement will be issued in the near future.

CLINICAL STUDY SITES LOCATED OUTSIDE THE UNITED STATES

FDA does not have jurisdiction over clinical study sites located outside the U.S. As a result, sponsors may proceed at these sites using their own discretion. FDA, however, encourages sponsors to follow a uniform protocol at the domestic and foreign investigational sites.

Although FDA does not have jurisdiction over clinical study sites located outside the U.S., FDA may accept, in support of a premarket approval application (PMA), the data generated from such sites. If the foreign clinical study was not conducted pursuant to the IDE regulation, the PMA regulation requires that the PMA applicant verify in the marketing application that the data generated from the foreign study site(s) are valid and that the investigators at the foreign sites conducted the studies in accordance with the "Declaration of Helsinki" and explain why the country's standards afforded greater protection to the human subjects.

United States Agents for Foreign Sponsors

As stated above, pursuant to 21 CFR 812.18(a), clinical studies conducted in the U.S. cannot be sponsored by foreign entities. Therefore, an IDE application cannot be approved in the absence of a U.S. sponsor. If an original IDE application is submitted from an entity outside the U.S., the application will be considered incomplete until a U.S. sponsor is identified. Similarly, if an IDE supplement is submitted for a proposed change in sponsorship to a foreign entity, the supplement will be disapproved.

GOOD MANUFACTURING PRACTICES

The current Good Manufacturing Practices (GMP) requirements set forth in the Quality System (QS) regulation are promulgated under section 520 of the Federal Food, Drug and Cosmetic (FFD&C) Act. They require that domestic or foreign manufacturers have a quality system for the design and production of medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. Thus, the QS regulation helps assure that medical devices are safe and effective for their intended use. The Food and Drug Administration (FDA) monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation.

The QS regulation is in Title 21, Code of Federal Regulations (CFR), Part 820. This regulation covers quality management and organization, device design, buildings, equipment, purchase and handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records. The preamble describes the public comments received during the development of the QS regulation and describes the FDA Commissioner's resolution of the comments. Thus, the preamble contains valuable insight into the meaning and intent of the QS regulation.

The Medical Device Quality Systems Manual: A Small Entity Compliance Guide, First Edition details the requirements of the new QS regulation and provides detailed guidance in the following areas:

1. obtaining information on GMP requirements;
2. determining the appropriate quality system needed to control the design, production an distribution of the proposed device;
3. designing products and processes;
4. training employees;
5. acquiring adequate facilities;
6. purchasing and installing processing equipment;
7. drafting the device master record;
8. noting how to change the device master records;
9. procuring components and materials;
10. producing devices;
11. labeling devices;
12. evaluating finished devices;
13. packaging devices;
14. distributing devices;
15. processing complaints and analyzing service and repair data;
16. servicing devices;
17. auditing and correcting deficiencies in the quality system; and
18. preparing for an FDA inspection.

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, and distribute devices that meet the quality system requirements. FDA has identified in the QS regulation the essential elements that a quality system shall embody for design, production and distribution, without prescribing specific ways to establish these elements. Because the QS regulation covers a broad spectrum of devices and production processes, it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices. For example, if it is impossible to mix up labels because there is only one label or one product, then there is no necessity for the manufacturer to comply with all of the GMP requirements under device labeling.

The medical device QS regulation requires an "umbrella" quality system intended to cover the design, production, and distribution of all medical devices from simple surgical hand tools to very complex computerized axial tomography (CAT) scanners. It is not practical for a regulation to specify details of quality system elements for such a wide range of products. Rather, the QS regulation specifies general objectives such as use of trained employees, design reviews, design validation, calibrated equipment, process controls, etc., rather than methods, because a specific method would not be appropriate to all operations.

In most cases, it is left to the manufacturer to determine the best methods to attain quality objectives. In some cases, however, the QS regulation does specify the particular type of method to be used, such as written procedures or written instructions. This does not mean, however, that manufacturers cannot vary from the method specified if the intent of the GMP requirement can be met by another method such as using an engineering drawing plus a model device as manufacturing instructions. Written procedures are not restricted to paper copies. Written procedures may be filed and distributed by automated data processing equipment. This flexibility is allowed by section 820.180.

Typically, large manufacturers will have a quality system that exceeds the medical device QS regulation. Small manufacturers will typically have a proportionally simpler system. FDA recognizes: that a small manufacturer may not need the same amount of documentation that a large manufacturer does in order to achieve a state-of-control; and, that some of the records maintained to fulfill the GMP requirements for written procedures may not be as long and complex for a small manufacturer.

After a manufacturer establishes a quality system, it should be maintained. Each manufacturer should assure that with growth and process or product changes their quality system is still adequate. This assurance is obtained through change control, day-to-day observance of operations, and by periodic audits of the quality system. The auditor should first identify the elements of the company's quality system. Next the audit should determine how well each element is functioning, and then determine its adequacy with respect to the intent of the device GMP requirements and meeting the company's quality claims.

Various manufacturers are exempt from the QS regulation or are not routinely inspected. However, these manufacturers are still subject to the FFD&C Act. If these manufacturers or any manufacturer render devices unsafe or ineffective, the devices are adulterated and/or misbranded and the manufacturers are subject to the penalties of the FFD&C Act.

FDA has determined that certain types of establishments are exempt from GMP requirements; and FDA has defined GMP responsibilities for others. Exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (21 CFR Part 820.198) or from general requirements concerning records (21 CFR Part 820.180).

POSTMARKET SURVEILLANCE/TRACKING

The Safe Medical Devices Act of 1990 (SMDA) amended the Federal Food, Drug and Cosmetic (FFD&C) Act increasing FDA's postmarketing regulation of medical devices. The two additional postmarketing activities include Postmarket Surveillance Studies and Device Tracking. Although the device criteria for postmarket surveillance and tracking are similar and the devices overlap, the intents are clearly twofold; postmarket surveillance is an early warning system after the initial marketing of a device while tracking is a system for locating potentially serious devices whether in distribution or with the user.

POSTMARKET SURVEILLANCE STUDIES

FDA may order manufacturers to conduct postmarket surveillance studies to gather safety and efficacy data for certain Class II and Class III devices. This requirement applies to any Class II and Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences; or
- which is intended to be implanted in the human body for more than one year; or
- which is intended to be a life sustaining or life supporting device used outside a device user facility.

Manufacturers must, within 30 days of receiving an order to conduct a postmarket surveillance study from FDA, submit, for approval, a plan for the required surveillance. The FDA may order a study for up to 36 months. Any longer period has to be mutually agreed upon by the manufacturer and FDA. If no agreement or a longer time period can be reached, then a dispute resolution process is to be followed.

After receiving the manufacturer's proposed plan, FDA has 60 days to determine if the person designated to conduct the surveillance is qualified and experienced, and if the plan will collect useful data that can reveal unforeseen adverse events or other information necessary to protect the public health.

DEVICE TRACKING

FDA has the discretion to order manufacturers of certain types of Class II or Class III devices to initiate a program to track their medical devices down to the patient level.

The types of devices subject to a tracking order may include any Class II or Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences, or
- which is intended to be implanted in the human body for more than one year, or
- which is intended to be a life-sustaining or life-supporting device used outside a device user facility.

In addition, patients receiving a tracked device may refuse to release, or refuse permission to release, their name, address, social security number, or other identifying information for the purpose of tracking.

MEDICAL DEVICE REPORTING

Since December 13, 1984, manufacturers and importers of medical devices have been required to comply with the Medical Device Reporting (MDR) regulation. The MDR requirements were changed in 1990, 1992, 1995 and again in 1997. Under the current provisions of the MDR regulation, which are found in 21 CFR Part 803, domestic and foreign medical device manufacturers and importers of medical devices are subject to the requirements.

The Food and Drug Administration (FDA) requires manufacturers and importers to report to FDA whenever the firm becomes aware of information that reasonably suggests that one of its marketed devices (1) has or may have caused or contributed to a death or serious injury, or (2) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The Medical Device Reporting (MDR) regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices so that problems may be detected and corrected in a timely manner.

The MDR regulation requires manufacturers of medical devices to report a device-related death, serious injury, or malfunction to FDA whenever they become aware of information that reasonably suggests that a reportable event occurred (one of their devices has or may have caused or contributed to the event). This is done using form FDA 3500A within 30 calendar days after becoming aware of the event. However, if the event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, then a report must be submitted within five (5) work days. These reports must also be submitted when FDA notifies a manufacturer that 5-day reports involving a particular type of medical device or type of event are required.

Manufacturers must submit baseline reports that provide basic device identification information including:

1. brand name,
2. device family designation,
3. model number,
4. catalog number, and
5. any other device identification number.

Baseline reports also contain other important information about the device including:

- regulatory basis for marketing the device,
- shelf life or expected life of the device, and
- date device was first marketed and when marketing stopped, if applicable.

A baseline report is to be submitted for a device when an adverse event involving the device is reported for the first time and is to be updated annually, when appropriate. FDA will allow annual updates to be done on the date which coincides with when a firm's annual registration is due instead of the anniversary date of the original baseline submission. The official dates for when an annual registration is due can be found in 21 CFR 807.21. Detailed instructions for completing the form can be found in the document entitled, "Instructions for Completing Form 3417 Medical Device Reporting Baseline Report." This is available on the MDR home page at www.fda.gov/cdrh/mdr.htm.

Manufacturers must submit a supplemental report, using Form 3500A, if they obtain additional information denoted as unknown (UNK) or not available (no information at the time, NI) on the original 30-day or 5-day MDR reports. Additionally, a supplemental report is required when new facts prompt the manufacturer to alter any information submitted in the original MDR report. The supplemental information must be submitted on Form 3500A within one month (30 calendar days) following receipt of the information.

In all, there are four types of MDR reports that FDA requires the manufacturer to submit. Each type of report is to be submitted within the mandatory time frame by completing the appropriate form. MDR reports for manufacturers include a :

1. 30-day report,
2. 5-ay report,
3. baseline report, and
4. supplemental report.

Manufacturers are required to establish and maintain files related to reportable events. The files must be prominently identified, facilitate timely access, and must contain:

- information related to the event or reference to the location of the information. This includes all documentation of the reporting decisions and decision-making process;
- copies of all completed MDR forms and other information submitted to FDA, importers (initial distributors), and manufacturers; and
- an explanation of why any required information was not submitted with the report or why it could not be obtained, and the results of the evaluation of the event.

Manufacturers must keep such records for two years, or a period of time equivalent to the expected life of the device, whichever is greater.

MEDWATCH

The MDR reporting program is one component of the total FDA adverse event and product problem reporting system. This system was renamed, "MedWatch – The FDA Medical Products Reporting Program" and was launched on June 6, 1993. The MedWatch program integrates onto a single reporting form, all of the adverse event and product problem reporting information required by the various FDA regulations. The program has both voluntary and mandatory components. The voluntary component encourages health care professionals to report serious adverse events

and product problems involving devices, drugs, biologics, special nutritional products and other products directly to the FDA. The mandatory component covers the adverse event and product problem reporting requirements currently in place for manufacturers of drugs, biologics and medical device manufacturers, distributors and user facilities.

PERFORMANCE STANDARDS

Under Section 514 of the FFD&C Act, FDA is authorized to develop and establish mandatory performance standards for Class II devices. Such standards may be developed by FDA or by outside organizations which offer to develop standards for FDA's consideration, or may be an existing standard that FDA adapts as its mandatory standard. If an FDA performance standard exists for a device, that device must conform to the standard before it can be legally marketed in the U.S. Regulations establishing a performance standard promulgated under Section 514 would not be effective before 1 year after the date of publication in the Federal Register, unless an earlier date is necessary for the protection of the public health and safety. Performance standards under Section 514 presently exist for Electrode Lead Wires and Patient Cables (21 CFR 898). There are standards for radiological devices, but they are not under Section 514.

RADIATION STANDARDS

In addition to performance standards that may be promulgated for medical devices under the FFD&C Act, CDRH may promulgate performance standards for radiation-emitting electronic products. So far, CDRH has developed performance standards for the following products:

- **Television Receivers** – This standard became effective January 15, 1970, and has been recodified in 21 CFR 1020.10. It applies to television receivers designed to receive and display a television picture, and includes electronic viewfinders on TV cameras, TV projectors, and TV monitors used with x-ray and other systems.

- **Diagnostic X-ray Equipment** – This standard became effective August 1, 1974, and has been recodified in 21 CFR 1020.30 through 1020.33, with subsequent amendments. It applies to complete diagnostic x-ray systems, as well as major components, including tube-housing assemblies, x-ray controls, high voltage x-ray generator, fluoroscopic imaging assemblies, x-ray tables, cradles, film changers, cassette holders, and beam-limiting devices.

- **Cabinet X-ray Systems** – This standard became effective April 10, 1976, and has been recodified in 21 CFR 1020.40. In addition to baggage inspection systems, it applies to other x-ray machines enclosed freestanding cabinets.

- **Laser Products** – This standard became effective August 1, 1976, and has been recodified in 21 CFR 1040.10 and 1040.11, with subsequent amendments. It applies to all lasers and products containing lasers. Specific requirements for medical lasers are in 21 CFR 1040.11(a).

- **Sunlamp Products and Ultraviolet Lamps Intended for Use in Sunlamp Products** – This standard became effective on May 7, 1980 and was amended September 8, 1986. It applies to all sunlamp products and ultraviolet lamps intended to induce suntanning.

- **Ultrasonic Therapy Products** – This standard became effective February 17, 1979, and has been recodified in 21 CFR 1050.10. It applies to any device intended to generate and emit ultrasonic radiation for therapeutic purposes at frequencies above 16 kilohertz, or any generator or applicator designed or specifically designated for use in such a device.

RADIATION-EMITTING ELECTRONIC PRODUCTS

Manufacturers of radiation-emitting electronic products listed in 21 CFR 1002.1 are required to submit product reports, abbreviated reports, annual reports and supplemental reports to CDRH under Section 536 of the FFD&C Act. These products fall into three groups:

- **Group A** – This group includes 4 categories of products: ultrasonic products, microwave heating equipment, high voltage vacuum switches, rectifier tubes, shunt regulator tubes, and cathode-ray tubes intended to be operated at voltages greater than 5,000 volts but less than 15,000 volts, and ultraviolet lamps and products containing such lamps intended for irradiation of any part of the living human body by light of wavelength in air less than 320 nanometers to perform a diagnostic or therapeutic function.

- **Group B** – This group includes 2 categories of products: television receivers that meet the federal standard, provided that the voltage on the tube and any other vacuum tube component cannot exceed 15,000 volts; and high-voltage vacuum switches, rectifier tubes, shunt regulator tubes, and cathode-ray tubes intended to be operated at voltages 15,000 volts or greater.

- **Group C** – This group includes 4 categories of products: products subject to Federal standards, except for television receivers which are in Group B above, diagnostic x-ray, cabinet x-ray, microwave ovens, laser products, sunlamp products, high intensity mercury vapor discharge lamps, and ultrasonic therapy products; products which are intended to produce x0radiation, including radiation therapy devices; industrial dielectric heaters, including radio frequency (RF) sealers and electromagnetic (EM) induction heating equipment that operate in the frequency range from 2 megahertz (MHZ) to 500 MHZ; and microwave diathermy machines.

CDRH has developed reporting guidelines for each of the products requiring such reports. These guidelines provide a detailed outline of the information required to be submitted and the reporting format. Reports should conform to the applicable reporting guideline or instruction to the extent that is possible or appropriate per 21 CFR 1002.10, .11 and .12.

Production or abbreviated reports must be submitted prior to the introduction of the product into commercial distribution in the U.S. Annual reports are to be submitted by September 1 of each year after the initial report and cover the 12 month period ending on June 30 preceding the due date. Supplemental, product or abbreviated reports of model changes which contain any changes in the information submitted to the product or abbreviated report must be submitted by the manufacturer prior to introducing a modified product into interstate commerce.

Additional Requirements

Manufacturers should also be aware 21 CFR 1002.20 concerning reporting of accidental radiation occurrences and 21 CFR 1003 through 1004, concerning actions required of manufacturers if products are found to have defects.

LABELING

The labeling of medical devices and in vitro diagnostic products are governed by two U.S. Federal laws:

- Fair Packaging and Labeling Act (FPLA)
- Federal Food, Drug and Cosmetic (FFD&C)Act

Most of the provisions of the FPLA and the FFD&C Act are codified in the following parts of Title 21 of the U.S. Code of Federal Regulations (CFR):

• General Device Labeling	21 CFR Part 801
• In Vitro Diagnostic Products	21 CFR Part 809
• Investigational Device Exemptions	21 CFR Part 812
• Good Manufacturing Practices	21 CFR Part 820
• General Electronic Products	21 CFR Part 1010

The FFD&C Act is the primary law under which the FDA takes action against non-complying regulated devices, such as adulterated, misbranded (mislabeled) devices. Section 201 of the FFD&C Act defines the terms "label" and "labeling" as they apply to medical devices and draws a distinction between the two terms. Certain provisions apply specifically to the "label" of the device, others are related to its "labeling". "Labeling" is a very broad term and deals with labels on the device as well as descriptive and informational literature that accompanies the device.

The FFD&C Act defines "label" as:

> a "display of written, printed, or graphic matter
> upon the immediate container of any article…".

The FFD&C Act defines "labeling" as:

> "all labels and other written, printed, or graphic matter
> (1) upon any article or any of its containers or wrappers, or
> (2) accompanying such article."

This labeling definition applies any time while a device is held for sale after shipment or delivery for shipment in U.S. interstate commerce. The term "accompanying" is interpreted liberally to mean more than physical association with the device. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, etc. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in U.S. interstate commerce.

Advertising is frequently considered by FDA to be labeling since the intent is to provide information about the device. General device labeling requirements consist of:

- Name, address and qualifier for manufacturer, packager or distributors;
- Intended use/directions for use;
- Prominence of labels;
- Over-the-counter (OTC) devices;
- Prescription devices;
- Labeling in English;
- Warning and caution statements; and
- Specific labeling for certain devices.

There are no requirements for FDA to review a device's label and/or labeling to confirm compliance with the labeling regulations above.

The device label and/or labeling is reviewed with the premarket notification or premarket approval submission, but strictly for indication for use statements and the demonstration of substantial equivalence and/or safety and effectiveness of the device.

When labeling does not meet the FDA regulations in 21 CFR Part 801, the device is considered to be misbranded. The following activities would cause a device to be misbranded:

- Its labeling is false or misleading in any particular, including promotion for unapproved uses;

- It is in package form and its label fails to contain the name and place of business of the manufacturer, packer, or distributor; and an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count;

- Any required wording is not prominently displayed as compared with other wording on the device, or is not clearly stated;

- Its label does not bear adequate directions for use including warnings against use in certain pathological conditions; or by children where its use may be dangerous to health; or against unsafe dosage, or methods, or duration of administration or application;

- It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended or suggested in the labeling; or

- It does not comply with the color additives provisions listed under Section 706 of the Act.

Compliance with the labeling regulations is enforced during postmarket activities such as GMP inspections of the facility.

MARKING-COUNTRY OF ORIGIN

Laws enforced by the U.S. Customs Service require that each imported article be legibly and conspicuously marked in English with the name of the country of origin. Exceptions to this rule are: articles which are merely in transit through the U.S.; articles which are otherwise specifically exempted from marking requirements. Certain articles may also require special marking.

If the article, or its container, when the container and not the article must be marked, is not properly marked at the time of importation, a marking duty equal to 10 percent of the customs value of the article will be assessed unless the article is exported, destroyed, or properly marked under U.S. Customs supervision before the liquidation of the entry concerned.

The country of origin must be marked and must be legible on the product that reaches the "ultimate purchaser." It is not feasible to state who the "ultimate purchaser" will be in every circumstance. However, broadly stated, an "ultimate purchaser" may be defined as the last person in the U.S. to receive the article in the form in which it was imported. Generally, if an imported article will be used in manufacture, the manufacturer is the "ultimate purchaser." If an article is to be sold at retail in its imported form, the purchaser at retail is the "ultimate purchaser. A person who subjects an imported article to a process which results in a substantial transformation of the article, even though the process may not result in a new or different article, may be an "ultimate purchaser," but if the process is merely a minor one which leaves the identity of the imported article intact, the consumer of the article is the "ultimate purchaser."

There are instances when an imported article is usually combined with another article after being imported, but before delivery to an "ultimate purchaser," and the name indicating the country of origin of the imported article appears so that it will be visible after such combining. In such cases, in addition to the name of the country of origin, the marking must include words or symbols which shall clearly show that the origin indicated is that of the imported article only, and **not** that of any other article with which the imported article may be combined after importation. An example is bottles, drums, or other containers imported empty, to be filled in the U.S. If they are marked to show the country of origin, they also must be marked with words such as "Bottle, drum or container made in (name of country)." Labels and similar articles so marked that the name of the country of origin of the article is visible after it is affixed to another article in this country shall be marked with additional descriptive words such as "Label made or printed in (name of country)" or words of similar nature.

Words or symbols in addition to the country of origin need not appear on articles of a kind which are ordinarily so changed in the U.S. that, in their changed condition, they become products of the U.S. For example, additional words or symbols are not required on toothbrush handles or hairbrush blocks which are to be used in the U.S. in the manufacture of brushes by inserting bristles in the blocks. It is permissible to mark articles or their containers with the name of the country of origin after importation. This is done under the U.S. Custom's supervision and at the expense of the importer. It almost always results in delay, inconvenience, and expense which could have been avoided had the articles or their containers been marked at the time of

manufacture. Specific information on marking can be obtained from U.S. Customs attaches or representatives abroad, from American consular officers or from the Commissioner of Customs, Washington, D.C. 20229.

PROCEDURES FOR THE EXPORT OF MEDICAL DEVICES FROM THE U.S.

Chapter VIII of the Federal Food, Drug and Cosmetic (FFD&C) Act addresses FDA regulation of the import and export of foods, drugs, cosmetics, biologics, medical devices, and radiation emitting electronic products. Sections 801 and 802 of Chapter VIII list the specific rules governing the import and the establishment of an Office of International Relations to act as FDA liaison with foreign governments. The basis for the regulation of imports and exports is contained in Chapter VIII of the FFD&C Act; in addition, a rule on the export of investigational devices is contained in 21 Code of Federal Regulations (CFR) 812.18 and a proposed rule (63 FR 64930) on the import-for-export provision of the FFD&C Act was published on November 24, 1998. In April 1996, Public Law 104-134, the "Food and Drug Export Reform and Enhancement Act of 1996" (FDERA), was signed into law by President Clinton. This law significantly modified Chapter VIII by enhancing the ability of U.S. firms to export unapproved FDA products **under certain conditions** without prior permission from FDA. The most notable change was the addition of provisions to and extension of section 802 to medical devices.

FDA has issued a February 1998 FDA guidance document on the FDA Export Reform and Enhancement Act of 1996, covering the import and export of FDA regulated products under FDERA. Documents references in this text are available on the FDA Internet site at www.fda.gov.

Export of Legally Marketed Devices

The export provisions of the FFD&C Act do not apply to firms who wish to export devices that are legally marketed in the U.S. Any medical device legally on the U.S. market may be exported anywhere in the world without prior FDA notification or approval. For a device to be legally in commercial distribution in the U.S., the following requirements must be met:

- The device site of manufacture must be registered with FDA on Form FDA 2891;
- Unless exempted by regulation or by having been on the market prior to May 28, 1976 (before the Medical Device Amendments to the FFD&C Act), commercial distribution in the U.S. of the device must be authorized by FDA through either a premarket notification [510(k)] or a premarket approval (PMA) application depending on the classification of the device;
- The device must meet the labeling requirements of 21 CFR Part 801;
- Unless exempted by regulation, the device must be manufactured in accordance with Good Manufacturing Practices (GMP) contained in the Quality Systems Regulation (QSR) of 21 CFR Part 820; and
- The device must be listed with FDA on Form FDA 2892.

Thus, the above would include preamendment devices, 510(k) exempt devices, devices which have a valid 510(k), and devices which have an approved PMA.

While FDA does not place any restrictions on the export of these devices, certain countries may require written certification that a firm or its devices are in compliance with U.S. law. In such instances, FDA will accommodate U.S. firms by providing a Certificate for Foreign Government (CFG). FDA has established this self-certification process in order to speed the processing of requests, which were formerly referred to as Certificates for Products for Export or Certificates of Free Sale.

Export Procedures for Unapproved Devices

Recent Changes

Until April 1996, the law that governed the export of medical devices not legally marketed in the U.S. was Sections 801(e)(1) and (e)(2) of the FFD&C Act. With passage of the FDERA, portions of Section 801 were modified. Section 802 was modified and its applicability was extended to include medical devices. Review the chart FDERA changes to Part VIII of the FFDCA in this chapter.

Exporting medical devices via section 801(e)(1)

A medical device which would be considered to be adulterated or misbranded, may be exported under Section 801(e)(1) of the FFD&C Act provided the device is intended solely for export. Although such a device would not meet the requirements of the FFD&C Act to be sold domestically for commercial distribution, it may be exported legally and without FDA permission in accord with Section 801(e)(1) provided the device is:

- in accord with the specifications of the foreign purchaser;
- not in conflict with the laws of the country to which it is intended for export;
- labeled on the outside of the shipping package that it is intended for export; and
- not sold or offered for sale in domestic commerce.

A medical device that has been sold or offered for sale in commercial distribution in the U.S. that is later determined to be adulterated or misbranded may not be exported under Section 801(e)(1) as an alternative to bringing the device into compliance with the requirements of the Act.

Unapproved Devices Due to Lack of 510(k) Marketing Clearance

The FDA is aware that in certain instances there may be devices which firms may wish to manufacture solely for export, or where they may wish to export during the interim period while their 510(k) premarket notification is under review. The FDA has allowed the export of unapproved devices which are adulterated because they lack 510(k) marketing clearance without prior clearance under its enforcement discretion if it meets two conditions:

- the device meets the requirements of 801(e)(1) listed above, and
- one would reasonably believe that the device could obtain 510(k) marketing clearance in the U.S. if reviewed by FDA.

This would include only devices which are identical in design, construction, and intended use to Class I or Class II devices or which the firm reasonably believes would be "substantially equivalent" to Class I or Class II devices. Devices which would not be included under this consideration are:

- Preenactment Class III devices for which FDA has called for the submission of a PMA,
- Postenactment Class III devices, i.e., placed on the market after May 28, 1976, or
- Devices evaluated by a firm and found to be **not substantially equivalent** to a 510(k)'d device.

In the past, many firms wished to market "for export only" an unapproved device which they reasonably believed could obtain a 510(k) and thus be exported under Section 801(e)(1) without prior FDA permission, but the foreign country or supplier insisted on being provided with a CFG. The FDA could not provide a CFG because the product had not undergone marketing clearance. Until the FDERA was enacted, the only way to obtain a CFG was to obtain U.S. marketing clearance. The FDERA added Section 801(e)(4) to Chapter VIII of the FFD&C Act. This section allows U.S. exporters to request from FDA a written certification that the device meets the applicable requirements of the FFD&C Act. FDA is thus directed to issue the certification within 20 days upon the firm's showing that the product meets the applicable requirements. FDA implemented a new certification process referred to as a Certificate of Exportability (COE) under Section 801(e)(1) to facilitate export of a medical device under 801(e)(1). Exporters applying for a COE are required to sign a statement indicating that they meet the four criteria of 801(e)(1) as detailed above. The making or submission of false statements are violations of United States Code Title 18, Chapter 47, Section 1001. Penalties for a false statement include up to $250,000 in fines and up to five years imprisonment. FDA will impose an initial fee of $100.00 per certificate and $10.00 per certificate for additional certificate(s) issued for the same product(s) on the same request. Original certificates will be provided on special counterfeit resistant paper with an embossed gold foil seal.

Unapproved Devices Due to Banning, Investigational Use or lack of PMA, would include: investigational devices, unapproved devices which would not be able to obtain a PMA (or whose PMA has not been approved), and banned devices. At the present time, synthetic hair fibers intended for implant are the only banned medical device. Prior to April 1996, the firms had only one option if they wished to export these devices, i.e., to export under Section 801(e)(2). Firms now have the additional option to export under 802 if their device meets certain criteria.

Exporting Medical Devices Via Section 801(e)(2)

In accord with Section 801(e)(2) of the FFD&C Act, four categories of misbranded and adulterated devices require a determination by FDA that exportation would not be contrary to public health as well as approval from an appropriate authority in the importing country, in addition to meeting the above criteria of Section 801(e)(1) of the FFD&C Act. These categories are:

- a device that does not comply with Section 514 (performance standards) of the FFD&C Act;
- a device that requires an approved PMA in accord with Section 515 of the FFD&C Act but does not have one;
- a device undergoing clinical investigation in accord with Section 520(g) of the FFD&C Act; and
- a device that is banned from the U.S. market under Section 516 of the FFD&C Act.

To obtain FDA's approval to export these devices in accord with Section 801(e)(2) of the FFD&C Act, a request that includes the following information should be submitted to FDA:

- A complete description of the device intended for export;
- The status of the device in the U.S.; e.g., whether it is investigational, banned, etc.; and
- A letter from the appropriate foreign liaison (person with authority to sign a letter of acceptance for the foreign government identified in the CDRH Foreign Liaison Listing), which must be either in English or accompanied by a certified English translation stating:

    1. the device is not in conflict with the laws of the country to which it is intended for export; (See the sample case study which follows for the situation where a country has no medical device laws.)
    2. the foreign government has full knowledge of the status of the device in the U.S.; and
    3. import is permitted or not objected to.

Section 801(e)(2) of the FFD&C Act states that FDA review export requests and determine that exportation of the device: (1) is not contrary to public health and safety and (2) has the approval of the country to which it is intended for export. Procedures recommend that the requester conduct a search of two databases or provide safety data.

(1) So that FDA may make the determination under the first statutory criterion – that export is not contrary to the public health and safety – manufacturers are instructed to submit with their export request (except as exempted below) basic data regarding the safety of the device.

There are two circumstances in which FDA does not recommend the submission of safety data with an export request:

- The device has an FDA approved investigational device exemption (IDE) and will be marked or used for clinical trials in the importing country for the same intended use; or
- The manufacturer has been informed by an Institutional Review Board (IRB) in the U.S. that the device is a non-significant risk device and the device will be marketed or used for clinical trials in the importing country for the same intended use.

(2) To determine whether the second statutory criterion of Section 801(e)(2) has been met – that exportation of the device has approval of the country to which it is intended for export – a letter from the foreign country approving importation (except as provided below) is required. Official foreign government liaisons are contained in the CDRH Foreign Liaison Listing.

If the manufacturer is exporting to a country within the European Economic Area (EEA) a device that has been awarded the "CE mark," FDA will accept documentation of the "CE mark" in lieu of a letter from the foreign government approving importation.

The requester should flag the request "Export Request" and send it, along with any questions concerning the export of medical devices, to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Information Processing and Office Automation Branch (HFZ-307)
2094 Gaither Road
Rockville, Maryland 10850
Telephone number: (301) 827-4555

Exporting Medical Devices Via Section 802

As an alternative to exporting medical devices under 801(e)(2), firms may now export Class III devices and devices required to meet a performance standard under Section 802 **if their form and their device meet certain criteria.** Below is a brief description of the requirements for exporting under Section 082, a detailed discussion is contained in the February 1998 FDA Guidance Document. The intent of the FDERA was to expedite the export of products which do not comply with U.S. law, but which are in compliance with the laws of foreign countries. The primary advantage to exporting under Section 802 instead of 801(e)(2) is that prior approval from FDA, i.e., submitting a request for and obtaining an Export Permit is not necessary in order to export. All that is required prior to export is for the firm to submit a "Simple Notification" as per Section 802(g). Under this notification, the firm must provide FDA with the name of the device and when they begin to export to a listed country(also referred to as a "Tier 1" country); for non-listed countries, they must provide notice of the device and country. No approval from FDA is required.

Section 802(b)(1) permits firms to export unapproved medical devices to countries other than Tier 1 countries if the device is authorized for sale in a Tier 1 country, and the importing country accepts that authorization. Some South American countries, for example, now permit marketing of any medical device with a CE mark.

The listed (or "Tier 1") countries are: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, a member of the European Union (United Kingdom, Spain, Ireland, Denmark, Greece, Germany, France, Italy, Luxembourg, Netherlands, Sweden, Finland, Belgium, Portugal and Austria), or the European Economic Area (includes the European Union countries and Norway, Iceland, and Liechtenstein).

in order to qualify for export under 802, devices must meet the four requirements of 801(e)(1) and pass the restrictions set forth in 802(f). They must:

- meet the requirements of Section 801(e)(1),
- substantially meet Good Manufacturing Practices (in the Quality Systems Regulation) or an international standard recognized by FDA,
- not be adulterated other than by the lack of marketing approval,
- not be the subject of a notice by DHHS that re-importation would pose an imminent hazard, nor pose an imminent hazard to the receiving country, and
- not be mislabeled other than by possessing the language, units of measure, or any other labeling authorized by the recipient country. In addition, the labeling must comply with the requirements and conditions of use in the listed country which gave marketing authorization, and must be promoted in accordance with its labeling.

The above is an abridged description of the requirements of 802(f). It is recommended that you consult the complete requirements in Section 802 of the FFD&C Act.

If the firm or device does not comply with the above criteria, the device cannot be exported under Section 802. The "Simple Notification," along with any questions concerning export of medical devices under Section 802, should be addressed to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Program Operations (HFZ-305)
2094 Gaither Road
Rockville, Maryland 20850
Telephone number: (301) 594-4520

Even though the FDA does not require a firm to obtain written permission prior to export, a firm may find itself in a situation where a foreign purchaser request proof of compliance with U.S. law prior to export. The FDA will also provide a Certificate of Exportability under Section 802 (COE) to facilitate export of a medical device under Section 802.

Additional Situations Where Export Permission is Automatically Granted Under Section 802

Devices used for investigational use – Medical devices may be exported under an Investigational Device Exemption (IDE), e.g., instances where clinical investigations are being conducted abroad. As per Section 802(c), the export of a medical device for investigational use in any Tier 1 country may be exported in accordance with the laws of that country and is exempt from regulation under the IDE statutory requirements of the FFD&C Act [Section 520(g)]. This is an abridged description of the requirements of 802(c). It is recommended that you consult the link at the header of this paragraph as well as the complete requirements in the Section 802 of the FFD&C Act.

Exported devices intended for further processing – As per Section 802(d), a medical device intended for further processing pending expected marketing authorization from a listed (Tier 1) country, may be exported for use in that country. The fundamental concept is that the device is being exported in anticipation of marketing approval. This is an abridged description of the requirements of 802(d). It is recommended that you consult the link at the header of this paragraph as well as the complete requirements in Section 802 of the FFD&C Act.

Devices intended for treatment of non-U.S. diseases – As per section 802(e)(1), a medical device intended for the diagnosis, treatment, or prevention of a tropical disease or another disease not prevalent in the U.S. which does not otherwise meet 802 criteria, may be exported with an FDA approved application for export if FDA finds that the device does not present:

- unreasonable risk,
- the benefits outweigh the risks, and
- the risks of using available alternatives was considered.

This is an abridged description of the requirements of 802(e)(1). It is recommended that you consult the link at the header of this paragraph as well as the complete requirements in Section 802 of the FFD&C Act.

The new FDA certification process (COE) also applies to export of a medical device under 802. Exporters applying for a COE are required to sign a statement indicating that they are exporting legally under the provisions of Section 802 as detailed above. False statements are violations of United States Code, Title 18, Chapter 47, Section 1001. Penalties for a false statement include up to $250,000 in fines and up to five years imprisonment.

Exporting for Investigational Use

A manufacturer who wishes to export an unapproved device for investigational use may export the device under an IDE, under Section 801(e)(2), or under 802(c) of the FFD&C Act depending on where, i.e., to what country, the device is being exported. For instance, pursuant to Section 801(e)(2) of the FFD&C Act, an unapproved device intended for investigational use may be exported to **any country**, if, in addition to meting the requirements of 801(e)(1) of the FFD&C Act, the exporter submits information to FDA that would enable the agency to determine that exportation is not contrary to the public health or safety and that the foreign country approves of the exportation.

Section 801(e)(1) of the FFD&C Act provides that a device intended for export should meet the following requirements: (1) complies with the laws of the foreign country; (2) meets the foreign purchaser's specifications; (3) is labeled for export on the shipping carton; and (4) is not sold or offered for sale in domestic commerce.

Alternatively, in accordance with Section 802(c) of the FFD&C Act, an unapproved device intended for investigational use may be exported **to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa or member countries of the European Union (EU) or the European Economic Area (EEA)** without FDA authorization if the unapproved device is

exported in accordance with the laws of that country. Devices being exported under 802(c) are not required to meet the requirements of the IDE regulation, however, compliance with the basic export requirements of 802(f) of the FFD&C Act and the record keeping requirements in 802(g) of the FFD&C Act is required. As explained above, exportation of an unapproved device for investigational use to any country other than the countries identified above requires authorization by FDA under Section 801(e)(2).

Exporting for Marketing or in Anticipation of Foreign Marketing Approval

Section 802(d) of the FFD&C Act permits the exportation of an unapproved drug, biologic, or device "intended for formulation, filling, packaging, labeling, or further processing in anticipation of market authorization" in any of the listed countries. The only express requirements for such exports are that the products comply with the laws of the foreign country and the requirements in Section 802(f) of the FFD&C Act. Records for such exports must be kept in accordance with Section 802(g) of the FFD&C Act. Details are included in the FDA Guidance for Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996, which is available at the FDA Website at www.fa.gov.

Import for Export

A firm may import device parts, components, subassemblies, etc. for further processing or incorporation into unapproved devices which are to be subsequently exported. A firm **may not** import a **finished** unapproved device without prior marketing clearance, even if the device is to be imported solely for subsequent export. The terms "further processing" and "incorporation" as detailed in the FDA Guidance for Industry is rather broad in its interpretation. For example, a device imported for further packaging or labeling would fall into this category; a device which is simply stored without any further action prior to export would **not** fall into this category.

Two detailed guidance documents exist on this subject; Chapter 9 of the Regulatory Procedures Manual and in the above referenced FDA Guidance for Industry which are also available on the FDA Website.

PART IV.

ELECTRONIC ACCESS TO FDA GUIDANCE DOCUMENTS AND INFORMATION

FDA ON THE INTERNET

The FDA World Wide Web site provides up-to-date, authoritative information on food, cosmetics, human and animal drugs, biologics, medical devices, and more.

To access the FDA Home Page, use this URL (uniform resource locator): *http://www.fda.gov*. From there you can easily locate consumer education materials, press releases, industry guidance, bulletins for health professionals, and a wealth of other useful documents and data from FDA's centers and offices.

Many agency components also have their own URLs. They include:

Center for Biologics Evaluation and Research: http://www.fda.gov/cber
Center for Devices and Radiological Health: http://www.fda.gov/cdrh
Center for Drug Evaluation and Research: *http://www.fda.gov/cder*
Center for Food Safety and Applied Nutrition:
    Foods Division: *http://vm.cfsan.fda.gov/list.html*
    Cosmetics Division: http://vm.cfsan.fda.gov/~dms/cos-toc.html
Center for Veterinary Medicine: http://www.fda.gov/cvm/
National Center for Toxicological Research: http://www.fda.gov/nctr/index.html
Office of Regulatory Affairs: http://www.fda.gov/ora/ora_home_page.html

FDA's Internet site replaces the agency's electronic bulletin board, which had provided on-line information for more than a decade. The Internet site offers far more material, in a more user-friendly form, including easy-to-use full-text searches and links to other FDA documents and other government Internet sites.

CDRH DOCUMENT RETRIEVAL SYSTEMS

The Division of Small Manufacturers Assistance (DSMA) was mandated by the 1976 medical device legislation to provide technical assistance and regulatory guidance to manufacturers to help them comply with Food and Drug Administration (FDA) requirements for medical devices. DSMA is located in the Center for Devices and Radiological Health (CDRH) within FDA. To contact DSMA staff for technical or regulatory assistance:

- Telephone **800.638.2041** or **301.443.6597**,
- Fax **301.443.8818**,
- Email **dsma@cdrh.fda.gov**, or
- Write to Division of Small Manufacturers Assistance (HFZ-220), Food and Drug Administration, 1350 Piccard Drive, Rockville, MD 20850-4307.

Manufacturers and others who are interested in the regulatory requirements for marketing medical devices and radiation-emitting electronic products can quickly obtain the latest information on operating policies and procedures through one of the following CDRH/DSMA document retrieval systems:

World Wide Web - FDA/CDRH maintains an entry on the World Wide Web (Web) for easy access to information. Information includes text, graphics, and files that may be downloaded to a PC with access to the Web. Updated on a regular basis, the CDRH Home Page includes the Quality Systems Manual, product classification database, device safety alerts, Federal Register reprints, information on cleared premarket submissions in a searchable database, small manufacturers' assistance, information on video conferencing and electronic submissions, mammography matters, and other device-oriented information. The CDRH home page may be accessed at **http://www.fda.gov/cdrh** and a self-service site for medical device and radiation emitting product information, "Device Advice", is located at **http://www.fda.gov/cdrh/devadvice**

CDRH Facts-On-Demand (F-O-D) - This automated system allows anyone to obtain CDRH information, 24 hours a day, 7 days a week by calling **800.899.0381** or **301.827.0111** from a touch-tone telephone. Using the telephone keypad and following the voice prompts, the caller can access the DSMA Facts section of CDRH F-O-D and request a DSMA Facts index **or** enter the three or four digit Shelf number for the desired document. The DSMA Facts index & documents that are less than 30 pages are put in queue to be automatically faxed to the fax number provided by the requester. Documents that are greater than 29 pages are faxed after normal business hours.

CDRH DOCUMENT RETRIEVAL SYSTEMS

DSMADOCs – Numerous documents are available in paper copy by mail. Submit your request for paper copy documents by either:

1. Email to: dsma@cdrh.fda.gov with the Subject = Publications, or
2. Fax to: Publications at 301.443.8818.

Include the Shelf_# of the documents being requested and your mailing address. A complete index, sorted four ways, is available; **1**. from the CDRH Web site, **2.** from CDRH Facts-On-Demand, or **3**. by Fax order, as noted in the table below.

Index Sort ß / Source Þ	**CDRH F-O-D**	**Fax Order**
Alphabetically on Title: dsmadoc.all	3913	3913
Shelf_#: dsmadoc.one	4913	4913
Document Date: dsmadoc.dat	5913	5913
Login Date: dsmadoc.log	6913	6913

CDRH Manuals on Disk

Disk - The following CDRH Manuals, also available on the CDRH Website at **http://www.fda.gov/cdrh/dsma/manuals.html**, are available at no cost from DSMA on 3.5" IBM formatted disks. Unless otherwise noted, the documents are in Word Perfect 6.1. To request one or more of these manuals on disk, check the appropriate box(es) below and either mail this page to DSMA (address on page 1) or fax it to **Publications** at **301.443.8818**. Limit one of each per firm. Disks may be freely copied and disseminated.

❑ Investigational Device Exemptions (IDE) Manual	July 1996
❑ Premarket Notification [510(k)] Manual	August 1995
❑ Medical Device Quality Systems (GMP) Manual	December 1996
❑ International Manual	April 1999
❑ Premarket Notification [510(k)] for In Vitro Devices Manual	January 1997
❑ Medical Device Reporting for Manufacturers Manual (MS Word 7.0)	March 1997
❑ Guidance for Industry and FDA; Medical Glove Guidance Manual, DRAFT	July 1999

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Country	