14 REGULATORY CONSIDERATIONS IN MEDICAL DEVICES

Scientific and technological advances in various fields, including medicine, pharmaceuticals, and biomaterials, have made it possible to develop new medical devices. Clinical applications of new medical devices and materials require appropriate testing for their safety and effectiveness. To ensure safety and effectiveness, manufacturers should assess various properties of the devices and materials using appropriate evaluation methods. The systematic evaluation of desired biological, chemical, and mechanical properties of devices and materials is necessary to provide the necessary information for long-term clinical applications. While chemical and mechanical evaluations can be done rather easily and reproducibly, biological evaluation has been difficult. This is mainly due to the lack of standard test methods that can be applied to various situations. Recently, the International Standards Organization (ISO) established international standard testing methods for biological evaluation. This is highly significant, since it implies, in principle at least, that manufacturers of medical devices and materials can perform their testing only once in a manner that satisfies regulatory bodies in all the countries in the world (Albert, 1997). In evaluation of medical devices and materials, the key question one should ask is whether a device or a material is "safe" and "effective." The safety and effectiveness are the two properties required for successful application of any medical device or material.

I. MEDICAL DEVICES AND MATERIALS

Hundreds of new medical devices are registered to Food and Drug Administration (FDA) every month. Each device is an improvement over the existing devices or an innovation. Medical device technology progressed rapidly in the wake of advances in polymers, metallurgy, ceramics, computers, engineering design, and nanotechnology. Of particular importance is the miniaturization technology, such as micromachining (*e.g.*, laser-cut stents, laser-drilled holes on medical devices), microelectromechanical systems (*e.g.*, miniature motors for precision delivery of infinitesimal amount of drugs from infusion devices), and microelectrochemistry. Many new biomaterials can be used to develop new medical devices for specialty application. For example, superporous hydrogel composites with fast swelling properties and good mechanical strength can be used to develop medical devices to treat aneurysms or cancer. In many instances,

development of new medical devices is closely followed by innovation in materials and technology.

A. Definition and Regulatory Classes of Medical Devices

The Food, Drug and Cosmetic Act (FD&C Act) of 1938 authorized FDA to regulate medical devices. The FD&C Act, however, did not require any type of premarket approval for medical devices. It simply provides FDA with authority to ensure proper labeling and to remove fraudulent devices from the marketplace (Mateo, 1996). The Medical Devices Amendments to the FD&C Act was signed into law on May 28, 1976, and under this law FDA has broad jurisdiction and authority over the commercialization of medical devices. The FDA authority was significantly expanded by the Safe Medical Devices Act of 1990, of which goal was to regulate medical devices in the premarketing and postmarketing stages with greater enforcement powers.

A medical device is defined as any instrument, apparatus, implement, machine, contrivance, implant, *in-vitro* reagent, or other similar or related article, including any component, part, or accessory

- which is recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and;
- which does not achieve any or its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes (U.S. Congress, 1938a)

Approximately 1,700 different generic types of medical devices, ranging from bandage to blood oxygenator, are classified and grouped into the 16 medical specialties referred to as panels (Table 14.1).

Each of the generic types of devices in Table 14.1 is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device (Table 14.2). Class I devices are not life-sustaining or life-supporting, and thus, are subject only to general controls (*i.e.*, establishment registration, device listing, device labeling, Good Manufacturing Practices. All Class I devices require a 510(k) pre-

Table 14.1 Device Classification Panels (or Specialty Groups)

Anesthesiology	General and Plastic Surgery
Cardiovascular	General Hospital and Personal Use
Clinical Chemistry and Clinical Toxicology	Neurology
Dental	Obstetrical and Gynecological
Ear, Nose, and Throat	Ophthalmic
Hematology and Pathology	Orthopedic
Immunology and Microbiology	Physical Medicine
Gastroenterology and Urology	Radiology

market notification unless individually exempted by the FDA, but do not normally require the submission of clinical data (Van Vleet, 1998). Class II devices require special control, such as special labeling requirements, mandatory performance standards, patient registries, and postmarket surveillance. In general, Class II devices require a 510(k) submission. Clinical data may be necessary if substantial equivalency claims are made. Class III devices are significant risk devices that may be either life-sustaining or life-supporting, or for a use substantially important in preventing impairment of human health. These devices require reasonable evidence of safety and efficacy before they can be legally marketed. An investigational device exemption (IDE) and a premarket approval (PMA) application with clinical data must be submitted for all Class III devices. Medical devices can be further categorized based on application methods (Table 14.3).

B. COMBINATION PRODUCTS

If a medical device is combined with a drug, a biological product, or both, it is called a combination product. According to the FD&C Act, FDA determines the primary mode of action of a combination product, and then designates a center within FDA to have primary jurisdiction over the premarket review. Usually, the primary FDA center jurisdiction is based on

Table 14.2 Three Regulatory Classes of Medical Devices

Class I Devices	Not life-sustaining or life-supporting (Examples: dental floss, surgical gloves, enema kit).
Class II Devices	Any devices for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls" (Examples: oxygen mask, blood pressure cuff, skull clamps, obstetric ultrasonic imager).
Class III Devices	Any devices that usually support or sustain human life (Examples: intraocular lens, heart valve, ventricular bypass device, and automated blood cell separator).

Table 14.3 Device Categories and Examples

Category		Example
Non-Contact Devices		*In-vitro* diagnostic devices
External Devices	Intact surfaces	Electrodes, external prostheses
	Breached or compromised surfaces	Ulcer, burn and granulation tissue dressings
Externally Communicating Devices	Intact natural channels	Contact lenses, urinary catheters, intravaginal and intraintestinal devices
	Blood path, indirect	Solution administration sets
	Blood path, direct	Intravenous catheters, oxygenators, dialyzers
Internal Devices	Bone	Orthopedic pins, plates, replacement joints, bone prostheses and cements
	Tissue and tissue fluid	Pacemakers, drug supply devices, biosensors, breast implants
	Blood	Heart valves, vascular grafts, internal drug delivery catheters

the intended use of the product. For example, an antibiotic-containing hip implant is intended to be used as a bone replacement and not as a drug or biologic. Thus, this implant is regulated as a device. Recent advances in tissue engineering have made it possible to produce new tissue engineered medical products, which are composed of complex and diverse materials and technology. Designation of the lead FDA center for product review is still based on the primary mode of action of the tissue engineered medical product, but additional center(s) assist in the evaluation in collaborative capacity. For example, cellular wound healing products incorporating a supportive matrix (*e.g.*, artificial skin) are treated as medical devices. Encapsulated cell therapies (*e.g.*, *ex vivo* liver assist devices) are evaluated jointly by Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH) with CBER as lead Center. Depending on the nature of the combination products, Center for Drug Evaluation and Research (CDER) can participate for joint evaluation. Currently, the standardization process for tissue engineered medical products is underway within the American Society for Testing and Materials (ASTM).

C. Medical Devices versus Drugs

Medical devices are distinguished from drugs for regulatory purposes in most countries based on mechanism of action. Medical devices operate via physical or mechanical means and are not dependent on metabolism to accomplish their primary intended effect (Witkin, 1998). Table 14.4 lists some differences between medical devices and drugs.

II. APPROVAL OF MEDICAL DEVICES AND MATERIALS

For marketing a medical device in the United States, manufacturers must go through one of two evaluation processes: premarket notification, unless exempt, or premarket approval (PMA).

A. Premarket Notification

Section 510(k) of the FD&C Act requires those device manufacturers who

Table 14.4 Differences of Medical Devices from Drugs

Medical devices are extremely diverse group of products varying widely in their intended use and principles of operation.
Medical devices are subject to frequent innovation in both design and use. Bench testing and animal models alone may validate new designs. Results from long-term clinical studies may no longer be relevant to current products and medical procedures.
Medical devices are used primarily by health-care professionals rather than by patients. The user cannot be blinded to the study intervention.
Medical devices are most often developed by small companies, and on a per product basis their annual sales are only a fraction of that for a typical pharmaceutical product. Practical considerations (regulations, financial constraints) limit new product development and testing.
The performance of any particular medical device is ultimately determined by the skill and clinical judgment of the user.

(Study Group, 1970)

must register to notify the FDA, at least 90 d in advance, of their intent to market a medical device. This is known as Premarket Notification, which is also called 510(k). The purpose of a premarket notification is to demonstrate that the medical device to be marketed is substantially equivalent to a legally marketed device that was or is currently on the U.S. market. It allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories. A premarket notification is also required if a device is reintroduced after significant change or modification that may have affected its safety or effectiveness. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use. Most medical devices are cleared for commercial distribution in the U.S. by the premarket notification process.

A premarket notification should include a table comparing substantial equivalence that identifies relevant similarities and differences in areas. Such areas include indications for use, target population, design, materials, performance, sterility, biocompatibility, mechanical safety, chemical safety, anatomical sites, human factors, energy used and/or delivered, compatibility with environment and other devices, electrical safety, thermal safety, and radiation safety. Side-by-side comparisons, wherever possible, are desirable.

B. Premarket Approval Regulations

Premarket approval regulations for medical devices require valid scientific evidence of safety and effectiveness provided by the manufacturers. Unlike for drugs, however, this evidence can come from sources other than well-controlled clinical investigations. Such sources include partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.

C. FDA Modernization Act of 1997

Section 201 of the FDA Modernization Act of 1997 allows sponsors of clinical studies of any Class III device to submit an investigational plan (including a clinical protocol) for early FDA review. This allows FDA to provide device sponsors with greater certainty about the appropriate clinical trial design and the scientific evidence necessary for achieving FDA approval (Kahan & Holstein, 1998).

III. STANDARDS FOR MEDICAL DEVICES AND MATERIALS

A. Standards

Consensus standards are documents that have been developed by committees to represent a consensus opinion on test methods, materials, devices, or procedures. In the United States, voluntary consensus standards are developed by a number of organizations. Committees within the Association for the Advancement of Medical Instrumentation (AAMI) develop

most standards in the areas of medical electronics, sterilization, vascular prostheses, and cardiac valves (Brown, 1996). The American Society for Testing and Materials Committee F-4 (ASTM F-4) develop most standards for the medical and surgical materials and devices. The ASTM F-4 main committee consists of several divisions: I on resources; II on orthopedic devices; III on medical/surgical devices; IV on tissue engineered medical products; and V on administrative. All the documents developed by AAMI and ASTM may then be reviewed and accepted by the American National Standards Institute (ANSI), which is the official U.S. organization that interacts with other national organizations to develop international standards within the ISO (Brown, 1996).

A test method standard describes the test specimen to be used, the conditions under which it is to be tested, how many are to be tested, and how the data are to be analyzed. A material standard describes the chemical and physical properties of the material. Implant materials must meet general biocompatibility test criteria. A device standard describes the device and its laboratory-based performance. General design aspects, dimensions, and dimensional tolerance are given using schematic drawings. The effectiveness and safety requirements of devices are stated in a device standard and not in a test method standard. A procedure standard describes how to handle samples, such as standard procedure for sterilizing the implantable devices (Brown, 1996). Table 14.5 shows examples of standards.

Standard test methods make it possible to reproduce results or verify the results by other researchers. In the area of medical devices and materials, standards can be used for physical, mechanical, chemical, and biological testing. Of the various testing of medical devices and materials, biological testing provides the most difficult challenges. Many biological testing methods have been well established, but there are still a large num-

Table 14.5 Examples of Voluntary Consensus Standards

Test Method Standards	
ADTM D638M	Test method for tensile properties of plastics (metric)
ASTM F746	Pitting and crevice corrosion of surgical alloys
ASTM D3124	Test method for vinylidene unsaturation in polyethylene by infrared spectroscopy
Materials Standards	
ASTM F451	Acrylic bone cements
ASTM F604	Silicone elastomers used in medical applications
Device Standards	
AAMI CVP3	Cardiac valve prostheses
AAMI RD17	Hemodialyzer blood tubing
ASTM F703	Implantable breast prostheses
ASTM F623	Foley catheters
Procedure Standards	
AAMI ROH-1986	Reuse of hemodialyzers
AAMI ST21	Biological indicators for ethylene oxide sterilization processes in health care facilities
ASTM F86	Surface preparation and marking of metallic surgical implants

ber of biological testing methods that should be standardized. For example, tests for the thrombogenicity (*i.e.*, the propensity for materials to cause blood coagulation) have not been standardized (Brown, 1996). Only guidelines for such tests have been developed by the NIH Heart Lung and Blood Institute.

IV. BIOLOGICAL EVALUATION OF MEDICAL DEVICES AND MATERIALS

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials, either directly or through the release of their material constituents, should not: produce adverse local or systemic effects; be carcinogenic; or produce adverse reproductive and developmental effects. Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

When selecting the appropriate tests for biological evaluation of a medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body. In general, the tests include: acute, sub-chronic and chronic toxicity; irritation to skin, eyes and mucosal surfaces; sensitization; hemocompatibility; genotoxicity; carcinogenicity; and, effects on reproduction including developmental effects. However, depending on varying characteristics and intended uses of devices as well as the nature of contact, these general tests may not be sufficient to demonstrate the safety of some specialized devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb cerebrospinal fluid. The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate. Sometimes biological evaluation of medical devices may have to be combined with functional test. For example, biosensors, such as implantable glucose sensors, may lose its sensibility quite rapidly after implantation. For medical devices for long-term implantation, fibrous capsules may form around the devices and this may reduce the efficacy for the intended applications.

Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all the tests suggested in the FDA matrix of this guidance. FDA reviewers are advised to use their scientific judgment in determining which tests are required for the demonstration of substantial equivalence under section 510(k). In such situations, the manufacturer must document

the use of a particular material in a legally marketed predicate device or a legally marketed device with comparable patient exposure.

A. Evolution of Simple Biological Testing into Biocompatibility Testing

Evaluation of the safety of new medical devices and materials was based on hosts of assays borrowed heavily from experiences with pharmaceutical screening. Naturally, some of them are irrelevant and completely inappropriate (Van Vleet, 1998). The first systematic approach to the determination of biological response of materials in the USA was described in 1961 (Autian, 1961). This scheme for testing was codified by the US Pharmacopoeia (USP) as biological reactivity tests of plastic containers (USP, 1965). Advances in polymer chemistry, medical devices, and biomaterials made it necessary to broaden the spectrum of types of tests beyond the concepts presented in USP.

For devices in direct contact with the patient or user, an exact identification and composition of all materials that contact the patient should be provided and a statement regarding any material differences from the legally marketed device should be explicitly stated. If the materials are identical to the legally marketed device and are identically processed and sterilized, then this should be stated. If the materials, manufacturing processes, and intended use are not identical or this information is not available for the legally marketed device, biocompatibility testing must be performed. Thus, manufacturers will need to provide biocompatibility test data for any new materials when the new device is compared to a legally marketed device of different materials. The data should be in a separate, identified biocompatibility section, be organized, and be complete.

1. Tripartite Biocompatibility Guidance and ISO-10993

The first attempt to identify and coordinate preclinical biocompatibility requirements for devices was released in 1986. It was the "Tripartite Biocompatibility Guidance" published by FDA to harmonize testing requirements in the U.S.A., Canada, and the United Kingdom. This document incorporates guidelines published by ASTM, FDA, USP, the Health Industry Manufacturers Association (HIMA), the American Dental Association, the British Standards Institute, and the European Confederation of Medical Suppliers Association (Van Vleet, 1998). In 1992, the ISO Technical Committee released the most complete and all-encompassing list of requirements for biological evaluation of medical devices (ISO, 1992). The FDA replaced the Tripartite agreement with this standard as of July 1, 1995 by issuing new guidance (FDA, 1995a). FDA is currently using the ISO-10993 Biological Testing of Medical and Dental Materials and Devices, in the evaluation of manufacturers' biomaterial testing program for medical devices. This guidance can be found in Office of Drug Evaluation (ODE) Bluebook Memorandum G95-1. The "Biological Evaluation of Medical Devices," ISO 10993 in 12 parts (Table 14.6) is the most comprehensive standard of preclinical device testing (Van Vleet, 1998), and it serves as one of the foundations of global harmonization (Marlowe, 1997). Tests in Table 14.6 are for evaluating interactive behavior between im-

Table 14.6 Biological Evaluation of Medical Devices (Contents of ISO 10993)

Part 1	Guidance on selection of tests
Part 2	Animal welfare requirements
Part 3	Tests for genotoxicity, carcinogenicity and reproductive toxicity
Part 4	Selection of tests for interaction with blood
Part 5	Tests for cytotoxicity: *in-vitro* methods
Part 6	Tests for local effects after implantation
Part 7	Ethylene oxide sterilization residues
Part 8	Clinical investigation (not part of EN 30993)
Part 9	Degradation of materials related to biological testing
Part 10	Tests for irritation and sensitization
Part 11	Tests for systemic toxicity
Part 12	Sample preparation and reference materials
	In Development
Part 13	Identification and quantification of degradation products from polymers
Part 14	Identification and quantification of degradation products from ceramics
Part 15	Identification and quantification of degradation products from coated and uncoated metals and alloys
Part 16	Toxicokinetic study design for degradation products and leachables
Part 17	Material characterization

plant material and living tissue (host response and the material response). Part 1 provides definitions and the guidance on selection of evaluation test categories that should be done. Parts 2–6 of the ISO 10993 provide more discussion and detail on the selection of individual tests that should be done for a particular biological interaction or biological effect. In general, the ISO documents do not provide details of test methods, but refer to other documents such as ASM and USP standards for procedures and methodology. New parts of the standard currently in development deal with test methods for identification and quantification of degradation products from materials.

The tests for leachables, such as contaminants, additives monomers, and degradation products must be conducted by choosing appropriate solvent systems that will yield a maximal extraction of leachable materials to conduct biocompatibility testing. The effects of sterilization on device materials and potential leachables, as well as, toxic by-products as a consequence of sterilization should be considered. Therefore, testing should be performed on the final sterilized product or representative samples of the final sterilized product. The importance of degradation and toxicokinetic studies in the design and development of medical devices can best be found through highly publicized commercial products, such as silicone gel breast implants, polyurethane-coated breast implants, pacemaker leads, hip implant wear debris, and drug-device combinations (Gott, 1997). Drug-device combinations necessitate toxicokinetic studies, which are the key link in establishing the safety and efficacy of the active ingredient in the device combination, with the data establishing its acceptability as a pharmaceutical under medicinal product regulations. Both systematic and local risks associated with the levels of the active material need to be evaluated (Gott, 1997).

2. Risk Assessments

Since it is virtually impossible to manufacture totally safe medical devices, some type of risk can be associated with every device and material. The process known as health-based risk assessment can be used to provide a justification for using materials that carry with them some element of risk (Stark, 1998). This is especially useful for materials that may be difficult to evaluate or be deemed unsuitable for medical applications under traditional biocompatibility testing regime. The first step in the risk assessment process is to identify the possible hazards that may be presented by a material (hazard identification). If a compound, an extract of the material, or the material itself is known to produce adverse effects, the dose response of the material should be determined (dose-response assessment). This provides information on the allowable limit, or the upper limit. This is followed by quantification of the available dose of the chemical residues that will be received by the patient (expose assessment). Finally, the allowable limit is compared with the estimated exposure to characterize the risk (risk characterization).

B. Clinical Trials

FDA recommends clinical trials for evaluation of the safety and effectiveness of diagnostic and/or therapeutic interventions (Kunitz, Gargano, & Kozloff, 1998). Approved devices are not subject to regulation by the FDA. Such studies are subject to Institutional Review Board (IRB) approval. Clinical trials of approved devices should be conducted in accordance with Good Clinical Practices (Segel, 1998). Clinical trials of investigational devices must be conducted according to the Investigational Device Exemption (IDE) regulations (FDA, 1995b). An IDE application must be submitted to the FDA and approved prior to commencing a clinical trial on a significant risk device (Segel, 1998). *In-vitro* diagnostic device are exempt from the IDE requirements if they are noninvasive, do not require an invasive sampling procedure that presents a significant risk, do not by design or intention introduce energy into a human subject, and are not used as a diagnostic procedure without confirmation of the diagnosis by another medically established product or procedure (FDA, 1995c). *In-vitro* diagnostic device are products that are intended for use in the collection, preparation, and examination of specimens taken from the human body (FDA, 1995d). All premarket approval (PMA) devices (*i.e.*, Class III devices that are not substantially equivalent to a pre-1976 device) require clinical research to support the determination of safety and effectiveness (Segel, 1998). Premarket notification devices (*i.e.*, devices that can be shown to be substantially equivalent to an approved device) generally require clinical research to support the determination of substantial equivalence (Segel, 1998). Supplemental application for extending labeling claims and/or modification of the intended use of the device requires clinical testing.

Medical devices do not have the same standards as drugs. There is a gap in the design of trials and number of trials between the two. U.S. Medical Device Amendments provided impetus to raise clinical trial

standards for devices. Scientific credibility and conclusion of safety and efficacy can be provided if at least two separate studies and at least two sites confirm results (Spilker, 1998). Confirmatory trial, however, is not yet a regulatory requirement in most countries.

One of the differences between evaluation of medical devices and drugs is that clinical outcomes observed in medical device studies are influenced not only by the product under evaluation and the patient, but also by the skill and discretion of the user (Witkin, 1998). The impact of the medical device user is a variable unique to medical device studies. This parameter can be responsible for the greatest degree of variability in the clinical outcomes measured. Clinical trial methods include a statement of a hypothesis, definition of a target population group, identification of patients and intervention characteristics (independent variables), and well-defined objective outcome measures (dependent variables or endpoints) (Kunitz, Gargano, & Kozloff, 1998). Outcome measures are a key component in the materials that the FDA uses to review and assess the safety and effectiveness of new devices (Kunitz, Gargano, & Kozloff, 1998). Before the 1970s, outcome was simply defined as a dichotomous variable, "dead" or "alive." New measures of physical function have evolved since then, and they include activities of daily living and disease specific scales for various diseases (Kunitz, Gargano, & Kozloff, 1998). Well-defined outcome measures can provide sponsors and FDA reviewers with evidence that the benefits of use outweigh the risks, and that the device will provide clinically significant effects (Kunitz, Gargano, & Kozloff, 1998). Approval of the device is usually limited to those areas whose outcomes are assessed. Table 14.7 shows classification of clinical studies of medical devices.

Table 14.7 Classification of Medical Device Clinical Studies

Pilot studies (or feasibility studies) of safety, performance, and/or design prior to marketing.	The first study of a novel investigational device in humans is usually a small pilot study undertaken to evaluate safety under carefully controlled conditions and to provide data in support of broader testing of performance in a larger population. This provides the first opportunity to evaluate the role of the user in device performance under actual clinical conditions.	
Pivotal trials of safety and effectiveness prior to marketing.	A single, well-controlled clinical trial of device performance remains sufficient for approval of a significant risk device by the FDA. These are prospective, analytical studies that provide objective evidence of effectiveness based on single, or in some cases multiple, clinical outcomes of significance.	
Postmarketing studies	Mandatory postapproval studies	Sponsors of Class III devices are required to conduct a "postapproval' clinical study as a mandatory condition for approval of premarket approval applications.
	Postmarket surveillance studies	The goal is to support expanded labeling claims and comparative performance claims, pharmacoeconomic, observational or analytical studies of specific safety or performance studies, and explant retrieval and failure analysis investigations.

(Witkin, 1998)

C. Observational Studies (Non-Experimental Studies)

The randomized controlled clinical trial, or experimental approach, is considered to be the "gold standard" for the evaluation of medical device safety and effectiveness (McTyre & Pottern, 1998). Such clinical trial constitutes the basis of the approval process for many medical devices (FDA, 1995e). There are, however, situations in which the clinical trial is either not feasible (owing to cost of practical limitations such as a rare disease) or unethical (as in circumstances where no alternative therapy exists) (McTyre & Pottern, 1998). In those situations, nonrandomized concurrent controlled trials or even observational studies based on sound historical data may be considered valid alternatives in the evaluation of devices (Sapirstein, Alpert, & Callahan, 1994). Observational studies or nonexperimental studies are defined as investigations that do not involve control by the researcher of the exposure experience or treatment intervention (McTyre & Pottern, 1998). Table 14.8 lists types of non-experimental studies.

D. Approval

The standard for approval of medical devices is more flexible than for drugs. The regulation requires "reasonable assurance" of safety and effectiveness, rather than the more onerous burden of 'substantial evidence" specified for drugs (Witkin, 1998; U.S. Congress, 1938b). The approval of drugs requires replication of clinical findings (*i.e.*, more than one clinical trial). On the other hand, approval of devices can be made with a single pivotal clinical trial. This is because the mechanism of action of a medical device results from product design and can be substantially verified by *in-vitro* performance testing (FDA, 1993; FDA, 1995f).

E. Implant Retrieval and Analysis

For the implantable medical devices, evaluation of retrieved implants offers the opportunity to investigate and study the intended use of medical devices. Significant improvements have been made through implant retrieval and analysis for medical devices, such as prosthetic heart valves, vascular grafts, cardiac-assist devices, orthopedic devices, and breast prostheses. Implant retrieval and evaluation programs allows determination of modes and mechanisms of implant failure or success (Anderson, 1996). Properly performed and systematic evaluations of explanted prosthetic de-

Table 14.8 Types of Observational Studies

Case series/Clinical follow-up approach	Case studies by clinicians and practitioners.
Case-control or retrospective approach	Comparisons are made between a group of subjects who have the outcome under investigation (cases) and a group who do not have the outcome (controls).
Cohort study approach	Groups of people (or cohorts), who have undergone an exposure (e.g., medical device or treatment) for which an evaluation is desired, can be used to investigate the relationship between medical devices and specific outcomes

Table 14.9 Steps for the Development of a New Medical Device

Materials selection and screening
Design and validation
Manufacturing validation
Performance testing
FDA approval
Post approval requirements

(Mueller, Ciarkowski, & McDermott, 1995)

vices lead to increasing knowledge (such as rates, morphologic features, and mechanisms) of device-related complications (Butany, 1997). In addition, these analyses explicate the structural basis of favorable performance and help predict the effects of future developments/modifications on device safety and efficacy (Butany, 1997). Such programs also offer the opportunity to determine the adequacy and appropriateness of animal models used in preclinical testing of medical devices. This information can be used to develop design criteria for future implantable devices. Implant retrieval and evaluation is a part of the continuous process of developing safer and more effective medical devices.

V. DEVELOPMENT AND EVALUATION PROCESSES

Development and evaluation of medical devices is not an easy task that anybody can take casually. Successful production of a medical device requires a group of people with an innovative idea, a clear goal and dedication. Quite often, smaller companies can focus more effectively on developing a medical device without any distraction. This may be one of the reasons that many medical devices are produced by small companies. In the United States, over 80% of medical device companies have less than 50 employees. While development and premarket evaluation of a new medical device is indeed an overwhelming process, it is something that can be managed. The level of effort put into development and evaluation of a medical device can be reduced if the long process can be deconvolved into smaller manageable units as listed in Table 14.9. In this deconvolution step, it is critically important to obtain information necessary for testing and evaluation of medical devices, and subsequent approval by the FDA. To promote the development of new medical devices, the governing agencies should provide all the information to those in need as quickly as possible. There has to be close communication between device manufactures and the responsible government agency.

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