Safety Evaluation in the Development of Medical Devices and Combination Products

Third Edition



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To Joyce, my wife, partner, and best friend, for all the light and joy that she has brought into my world.

Shayne Cox Gad

To Mickey with love—you are the compass that guides me, the ballast that keeps me afloat, and the wind in my sails.

Marian McCord

Preface to the Third Edition

This third edition of Safety Evaluation of Medical Devices, while continuing to focus on the objective of the earlier editions (to serve as a single-volume practical guide for those who are responsible for or concerned with ensuring safety in the use and manufacture of medical devices) also reflects the significant changes brought about since the last (second) edition some six years ago. It not only updates throughout, but also adds extensive coverage of combination products and case histories of current real life problems in the field.

Foremost, this new edition has been recast throughout to address the fact that device markets are global, that technology continues to advance, and that device safety regulation has been increasingly harmonized. Each aspect of device safety evaluation is considered in terms of International Standards Organization (ISO), U.S. Food and Drug Administration (FDA), European Union (EU), and Japanese Ministry of Health and Welfare (MHW) perspectives. Additionally, the continuing growth of technology has led to the incorporation of science (particularly in the areas of immunotoxicology and toxicokinetics). Also incorporated are new case examples and citations with the means of access to Internet-based regulatory and scientific sites, reflecting the universal adoption of this technology into our world.

Shayne C. Gad
Marian G. McCord

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Introduction

The medical device industry in the United States and worldwide is immense in its economic impact (sales in 2006 were $220 billion worldwide and $114 billion in the United States, $60 billion in the European Community and $32 billion in Japan), scope (between 92,000 and 145,000 different devices are produced in the U.S. by ~12,000 different manufacturers employing some 370,000 people; it is believed that ~2,100 of these manufacturers are development stage companies without products yet on the market) and importance to the health of the world's citizens (The Wilkerson Group, 2006). The assessment of the safety to patients using the multitude of items produced by this industry is dependent on schemes and methods which are largely particular to these kinds of products, not as rigorous as those employed for foods, drugs, and pesticides, and which are in a state of flux. Regulation of such devices is, in fact, relatively new. It is only with the Medical Device Amendments (to the Food, Drug and Cosmetic Act) of 1976 that devices have come to be explicitly regulated at all. And with the Safe Medical Devices Act of 1990, the Medical Device Amendments of 1992 and subsequent laws that the regulation of devices for biocompatibility became rigorous.

The causes behind this timing are reviewed in the case histories presented in the last chapter of this book.

For purposes of this book, the safety we are concerned with is that related to the biological and chemical interactions of devices with patients' bodies, and not that due to mechanical or structural malfunction (such as structural failure of heart valves and pacemakers). Such safety, also referred to as biocompatibility, only became of general concern to the public with publicity around plasticizers in devices and increased mortality with cardiovascular stents. Earlier cases of perceived significant risk on the part of devices (the Dalkon Shield intrauterine device, silicones in breast implants, and latex present in gloves and a wide range of other devices) largely faded from public and professional memory by the beginning of the 21st century.

BIOCOMPATIBILITY

A medical device that is adequately designed for its intended use should be safe for that use. The device should not release any harmful substances into the patient which can lead to adverse effects. Some manufacturers believe that biocompatibility is sufficiently indicated if their devices are made of medical grade material, or materials approved by FDA as direct or indirect additives. The term "medical grade" does not have an accepted legal or regulatory definition and can be misleading without biocompatibility testing. Likewise, the existence of a material master file (MMF) does not provide any assurance as to what biocompatibility data (or of what quality) is available. More to the point as the extent of required data and testing is expanded, what constitutes adequate testing is a moving target as time passes.

There is no universally accepted definition for biomaterial and biocompatibility. Yet the manufacturer who ultimately markets a device will be required by FDA to demonstrate biocompatibility of the product as part of the assurance of its safety and effectiveness. The manufacturer is responsible for understanding biocompatibility tests and select methods which best demonstrate

- the lack of adverse biological response from the biomaterial, and
- the absence of adverse effects on patients.

Diversity of the materials used, types of medical devices, intended uses, exposures, and potential harms present an enormous challenge to design and conduct well-defined biocompatibility testing programs. Experience gained in one application area is not necessarily transferable to another application. The same applies to different or sometimes slightly different (variable) materials. Biodegradation and interaction of materials complicates safety considerations, as does the increased scope of combination device drug products.

Biocompatibility describes the state of a biomaterial within a physiological environment without the material adversely affecting the tissue or the tissue adversely affecting the material. Biocompatibility is a chemical and physical interaction between the material and the tissue and the biological response to these reactions.

Biocompatibility assays are used to predict and prevent adverse reactions and establish the absence of any harmful effects of the material. Such assays help to determine the potential risk which the material may pose to the patient. The proper use of biocompatibility tests can reject potentially harmful materials while permitting safe materials to be used for manufacturing the device.

Any biocompatibility statement is useful only when it is considered in the proper context. A statement such as "propylene is biocompatible" lacks precision and can lead to misunderstanding. Any statement of biocompatibility should include information on the type of device, intended conditions of use, degree of patient contact, and the potential of the device to cause harm. Manufacturers should avoid using the term "biocompatible" without clearly identifying the environment in which it is used and any limitations on such.

The need for biocompatibility testing and the extent of such testing that should be performed depends on numerous factors which are presented and considered in Chapter 2. These factors include the type of device, intended use, liability, degree of patient contact, nature of the components, and potential of the device to cause harm. There are no universal tests to satisfy all situations, and there is no single test which can predict biological performance of the material

or device and reliably predict the safety of the device. The types and intended uses of medical devices determine the types and number of tests required to establish biocompatibility. Biological tests should be performed under the condition which simulates the actual use of the product or material as closely as possible and should demonstrate the biocompatibility of a material or device for a specific intended use. These tests will be more extensive for a new material than for those materials that have an established history of long and safe uses.

All materials used in the manufacture of a medical device should be considered for evaluation of their suitability for intended use. Consideration should always be given to the possibility of the release of toxic substances from the base materials, as well as any contaminants which might remain after the manufacturing process or sterilization. The extent of these investigations will vary depending on previously known information (prior art) and initial screening tests.

Fundamentals of Biocompatibility Tests

Biocompatibility is generally demonstrated by tests utilizing toxicological principles which provide information on the potential toxicity of materials in the clinical application. Many classical toxicological tests, however, were developed for a pure chemical agent, and are not applicable to biocompatibility testing of materials. In addition, medical devices are an unusual test subject in toxicity testing. A biomaterial is a complex entity, and the material toxicity is mediated by both physical and chemical properties. Toxicity from biomaterial often comes from leachable components, and the chemical composition of a material is often not known. Toxicological information on the material and its chemical composition is seldom available, and the possible interactions among the components in any given biological test system are seldom known.

Biocompatibility cannot be defined by any single test. It is highly unlikely that any single parameter will be able to ensure biocompatibility. Therefore, it is necessary to test as many biocompatibility parameters as appropriate to develop a matrix of information. It is also important to test as many samples as possible. Therefore, suitable positive and negative controls should produce a standard response index for repeated tests. Additionally, the use of exaggerated conditions, such as using higher dose ranges and longer contact durations or multiple insults that are may factors more severe than the actual use condition, is important. Identifying and subsequently ensuring an acceptable exposure level that is multiple factors below the lowest toxic level is the general and expected practice.

Most of the basic biocompatibility tests are short-term tests to establish acute or short-term toxicity. Data from these short-term tests should not be stretched to cover the areas where no test results are available.

Biocompatibility testing should be designed to assess the potential adverse effects under actual use conditions or specific conditions close to the actual use conditions. The physical and biological data obtained from biocompatibility tests should be correlated to the device and its use. Accuracy, reproducibility, and interpretability of tests depend on the method and equipment used and the investigator's skill and experience.

There are several toxicological principles which the investigator must consider before planning biocompatibility testing programs. Biocompatibility depends on the tissue that contacts the device. For example, the requirements for blood-contacting device would be different from those applicable to a urethral catheter. Also, the degree and nature of required biocompatibility assurance depends on the nature, extent and duration of contact with the human body. Some materials, such as those used in orthopedic implants, are meant to last for a long period in the patient. In this case, a biocompatibility testing program needs to show that the implant does not adversely affect the body during the long period of use. The possibility of biodegradation of material or device can not be ignored, and evaluation of such is now required by ISO-10993 guidances.. Biodegradation by the body can change an implant's safety and effectiveness. The leachables from plastic used during a hemodialysis procedure may be very low, but the patient who is dialyzed three times a week may be exposed to a total of several grams during their lifetime. Therefore, cumulative effects (chronicity) should be assessed.

Two materials having the same chemical composition but different physical characteristics may not induce the same biological response. The nature of the tissue to device interface (is the device surface smooth textured or rough?) is very important. Also, past biological experiences with seemingly identical materials also has possible limited toxicity. Toxicity can arise from leachable components of the material due to differences in formulation and manufacturing procedures.

Empirical correlation between biocompatibility testing results and actual toxicity findings in humans and the extrapolation of the quantitative results from short-term in vitro tests to quantitate toxicity at the time of use are controversial. These need careful and scientifically sound interpretation and adjustment. The control of variation in biological susceptibility and resistance to obtain a biological response range for toxic effect, and host factors which determine the variability of susceptibility in toxicological response adjustment to susceptibility in the human population also need careful attention.

The challenge of biocompatibility is to create and use knowledge to reduce the degree of unknowns and to help make the best possible decisions. The hazard presented by a substance, with its inherent toxic potential, can only be manifested when fully exposed in a patient. Therefore, risk, which is actual or potential harm, is a function of toxic hazard and exposure. The safety of any leachables contained in the device or on the surface can be evaluated by determining the total amount of potentially harmful substance, estimating the amount reaching the patient tissues, assessing the risk of exposure, and performing the risk *versus* benefit analysis. When the potential harm from the use of biomaterial is identified from the biocompatibility tests, this potential must be compared against the availability of an alternate material.

SCOPE OF DEVICES AND THE MEDICAL DEVICE MARKET

According to section 201(h) of the Food, Drug and Cosmetic Act, a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory that is:

- Recognized in the official *National Formulary*, or the *United States Pharmacopoeia* (USP, 1994), or any supplement to them.

Intended for use in the diagnosis of disease, in man or other animals, or
- Intended to affect the structure or any function of the body or man or other animals, and which does not achieve any of its primary 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 (CDRH, 1992).

Under this definition, devices might be considered as belonging to one of eight categories (North American Industrial Classification): surgical and medical instruments, ophthalmic, dental, laboratory apparatus, irradiation, specialty devices, medical/surgical supplies, in vitro diagnostics, and electromedical. There are (in 2000) 16,170 companies involved in these sectors—6750 of them manufacture worldwide. This is a global industry with a $220 billion annual market. The US market is $114 billion, or 52% of this (MDDI, 2000).

The top twenty medical devices by revenues in 1999 were:

1. Incontinence supplies
2. Home blood glucose monitoring products
3. Wound closure products
4. Implantable defibrillators
5. Soft contact lenses
6. Orthopedic fixation devices
7. Pacemakers
8. Examination gloves
9. Interventional cardiovascular coronary stents
10. Arthroscopic accessory instruments
11. Prosthetic knee joint implants
12. Lens care products
13. Prosthetic hip joint implants
14. Multiparameter patient monitoring equipment
15. Mechanical wound closure
16. Wound suture products
17. Absorbable polymers
18. Hearing aids
19. Wheelchair and scooter/mobility aids industry
20. Peritoneal dialysis sets.

The ten projected biggest growth device products (in 2000) are shown in Table 1.1.

HISTORY

As has previously been reviewed by Hutt (1989), the regulation of medical devices has followed a different history than that of drugs. Medical devices go back to at least the Egyptians and Etruscans. Problems with fraudulent devices in the United States date back to the late 1700s, though no legislative remedy was attempted until the 1900s. In fact, the legislative history of the 1906 Food and Drug Act contains no references to devices. Devices continued to be regulated under the postal fraud statutes. Such regulation was evidently ineffectual, as fraudulent devices flourished during this period. Starting in 1926, the Food and Drug Administration (FDA) monitored such devices and assisted the U.S. Postal service in its regulatory actions. Medical devices were covered in the 1938 Act, but only in regard to adulteration and misbranding. Over the intervening years, various committees which examined medical device regulation consistently came to similar conclusions: that the FDA has inadequate authority and resources to regulate the medical device industry. As part of the agreement that resulted in passage of the 1962 amendments, however, all references to medical devices were deleted. The need and demand for increased regulation continued to grow. In 1967, President Lyndon Johnson supported the proposed Medical Device Safety Act, which nevertheless was not well received by Congress. In fact, no legislation pertaining to medical device safety was passed until 1976.

In 1969, at the request of then President Richard Nixon, the Department of Health, Education and Welfare (HEW) established a Study Group in Medical Devices, also known as the Cooper Committee, because it was chaired by the Director of the National Heart and Lung Institute, Dr. Theodore Cooper. Its report in 1970 concluded that a different regulatory approach was needed to deal with medical devices. This report initiated the chain of events that culminated in the Medical Device Amendment of 1976. In the interim, the Bureau of Medical Devices and Diagnostic Products was created in 1979. Remarkably, the 1976 Amendment retained the essential provisions of the Cooper Committee Report regarding inventory and classification of all medical devices by class: Class I (general controls), Class II (performance standards), or Class III (premarket approval). These classifications are discussed in greater detail later in this chapter. These remain the essential regulations applicable to medical devices. Both the Drug Price Competition and Patent Restoration Act of 1984 and the Orphan Drug Act of 1983 contained language that made the provisions of the laws applicable to medical devices but did not have provisions unique to medical devices. The recent perceptions, revelations, and controversy surrounding silicone breast implants will probably cause additional changes in the regulation of devices.

Table 1.1 Highest Revenue Growth Products

Rank	Product	Revenue Growth Rate (%) (yrs)	Specialty
1	Fibrin sealants	174.6 (95-02)	Wound care
2	Solid artificial organs	141.2 (95-02)	Transplant/implant
3	Left ventricular assist devices	96.0 (95-02)	Cardiovascular
4	Skin substitute products	63.1 (97-04)	Wound care
5	Refractive surgical devices	54.4 (98-05)	Ophthalmic
6	Gynecologic falloposcopes	49.5 (95-00)	Endoscopic/MIS
7	PTMR products	47.8 (00-04)	Cardiovascular
8	Bone growth substitutes and growth factors	47.0 (97-04)	Orthopedics
9	Growth factor dressings	46.0 (97-04)	Wound care
10	Vascular stent-grafts	46.0 (97-04)	Cardiovascular

Source: Frost and Sullivan.

As a consequence, 1978 brought guidelines for investigational device exemptions (IDEs, the equivalent of INDAs for drugs). These requirements, as shall be seen later, effectively excluded a wide range of medical devices from regulation by establishing an exemption for those new or modified devices which are equivalent to existing devices. The year 1990 saw the passage of the Safe Medical Devices Act, which made premarketing requirements and postmarketing surveillance more rigorous. The actual current guidelines for testing started with the USP guidance on biocompatibility of plastics. A formal regulatory approach springs from the Tripartite agreement, which is a joint intergovernmental agreement between the United Kingdom, Canada, and the United States (with France having joined later). After lengthy consideration, the FDA has announced acceptance of International Standards Organization (ISO) 10993 guidelines for testing (ASTM, 1990; FAO, 1991; MAPI, 1992; O'Grady, 1990; Spizizen, 1992) under the rubric of harmonization. This is the second major trend operative in device regulation: the internationalization of the market place with accompanying efforts to harmonize regulations. Under ICH (International Conference on Harmonization) great strides have been made in this area.

Independent of FDA initiatives, the USP has promulgated test methods and standards for various aspects of establishing the safety of drugs (such as the recent standards for inclusion of volatiles in formulated drug products), which were, in effect, regulations affecting the safety of drugs and devices. Most of the actual current guidelines for the conduct of nonclinical safety evaluations of medical devices have evolved from such quasi-agency actions (such as the USP's 1965 promulgation of biological tests for plastics and ongoing American National Standards Institute (ANSI) standard promulgation).

Public concerns about three specific device safety issues have seemed to increase regulatory scrutiny. The first of these, the Dalkon Shield, was an intrauterine contraceptive device produced by the A. H. Robbins Corporation (Sivin, 1993). Its use was associated with unacceptable rates of pregnancy, pelvic inflammatory disease, and death in women who used it. The device was withdrawn from the market in 1974, and in 1988 Robbins reached a $3.3 billion settlement in response to a class action suit (Nocera, 1995).

The second case is that of silicone-filled breast implants, which have been purported to cause a range of autoimmune and neurologic effects on some women who have them. Though the validity of these claims remains unproven or disproven, litigation over them drove the primary manufacturer (Dow Corning) into bankruptcy and lead to the removal of these products from the market (though, in 2006, they have returned to the market). Since the late 1980s concern has grown about allergic responses to latex in devices. Several deaths have been blamed on anaphylactic responses to such effects (Lang, 1996). In the current century, potential male reproductive effects from DEHP leaching from medical devices and leading to removal of such products from the market place.

NONSPECIFIC REGULATORY CONSIDERATIONS

A broad scope review of regulatory toxicology is presented in Gad (2001). Some necessity to understand regulations beyond those covered in Chapter 2 requires review here, however.

Good Laboratory Practices

The original promulgation of GLPs was by the U.S. FDA in 1978 in response to a variety of cases which led the agency to conclude that some of the data that it had obtained in support of product approvals were not trustworthy. Subsequently, other regulatory agencies and authorities in the United States and across the world have either promulgated their own version of similar regulations or required adherence to the set generated by the U.S. FDA or another body. The EEC requirement for compliance with GLPs for safety tests has recently been reinforced in a modification of Directive 75/318/EEC (Regulatory Affairs Focus, 1996; ISO, 1990; European Committee for Standardization, 1991). The FDA last revised the GLP regulations in 1989 (FDA, 1989), but is currently (July, 2008) working on a revision.

The GLPs require that all pivotal preclinical safety studies—that is, those that are used and regulatorily required to make decisions as to the safety of the product (in our case, a device)—conducted under a well-defined protocol utilizing procedures set forth in written standard operating procedures by trained (as established by documentation) personnel under the direction of a study director. All work must be reviewed by an independent Quality Assurance Unit (QAU). The regulations require rigorous attention to record keeping, but do not dictate how actual studies are designed or conducted in a technical sense (Gad and Taulbee, 1996).

Animal Welfare Act (AWA)

Gone are the days when the biomedical research scientist could conduct whatever procedures or studies that were desired using experimental animals. The Animal Welfare Act (APHIS, 1989) (and its analogues in other countries) rightfully requires careful consideration of animal usage to ensure that research and testing uses as few animals as possible in as humane a manner as possible. As a start, all protocols must be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC) prior to animals being ordered or a study being initiated. Such review takes time, but should not serve to hinder good science. When designing a study or developing a new procedure or technique, the following points should be kept in mind:

1. Will the number of animals used be sufficient to provide the required data, yet not constitute excessive use? It ultimately does not reduce animal use to utilize too few animals to begin with and then have to repeat the study.
2. Are the procedures employed the least invasive and traumatic available? This practice is not only required by regulations, but is also sound scientific practice, since any induced stress will produce a range of responses in test animals that can mask or confound the chemically induced effects.

Most recently (September of 2000) USDA (which administers the AWA) had decided to begin including rodents in all aspects of the AWA's reporting requirements.

Regulations Versus Law

A note of caution must be inserted here. The law (the document passed by Congress) and the regulations (the documents written by the regulatory authorities to enforce the laws) are separate documents. The sections in the law

do not necessarily have numerical correspondence. For example, the regulations on the PMA process are described in 21 CFR 312, but the law describing the requirement for a PMA process is in Section 515 of the FDLI. Because the regulations rather than the laws themselves have a greater impact on toxicological practice, greater emphasis is placed on regulation in this chapter. For a complete review of FDA law, the reader is referred to the monographs by Food and Drug Law Institute in 1995 (FDLI, 1995).

Laws authorize the activities and responsibilities of the various federal agencies. All proposed laws before the U.S. Congress are referred to committees for review and approval. The committees responsible for FDA oversight are summarized in Table 1.2. This table also highlights the fact that authorizations and appropriations (the funding necessary to execute authorizations) are handled by different committees. Figure 1.1 presents the organization of the Center for Devices and Radiological Health (CDRH). As can be seen by the organizational structure presented in the figure, the categorization of devices for division review purposes is functionally based.

Table 1.2 Congressional Committees Responsible for FDA Oversight

Authorization	
Senate	All public health service agencies are under the jurisdiction of the Labor and Human Resources Committee.
House	Most public health agencies are under the jurisdiction of the Health and the Environmental Subcommittee of the House Energy and Commerce Committee.
Appropriation	
Senate	Unlike most other public health agencies, the FDA is under the jurisdiction of Agriculture, Rural Development, and Related Agencies Subcommittee of the Senate Appropriations Committee.
House	Under the jurisdiction of the Agriculture, Rural Development, and Related Agencies Subcommittee of the House Appropriations Committee.

ORGANIZATIONS REGULATING DRUG AND DEVICE SAFETY IN THE UNITED STATES

The agency formally charged with overseeing the safety of drugs and devices in the United States is the FDA. It is headed by a commissioner who reports to the Secretary of the Department of Health and Human Services (DHHS) and has a tremendous range of responsibilities. Medical devices are overseen by the CDRH, headed by a director. Drugs are overseen primarily by the Center for Drug Evaluation and Research (CDER) (though some therapeutic or health care entities are considered as biologically derived and therefore regulated by the Center for Biologic Evaluation and Research, or CBER). There are also "combination products" (part drug, part device) which may be regulated by either or both CDER/CBER and CDRH, depending on the principal mode of action (PMOA) of the product.

Most of the regulatory interaction of a toxicologist involved in assessing the biocompatibility of devices is with the appropriate part of the CDRH, though for combination products the two centers charged with drugs or biologicals may also come into play. Within the CDRH there is a range of groups (called divisions) which focus on specific areas of

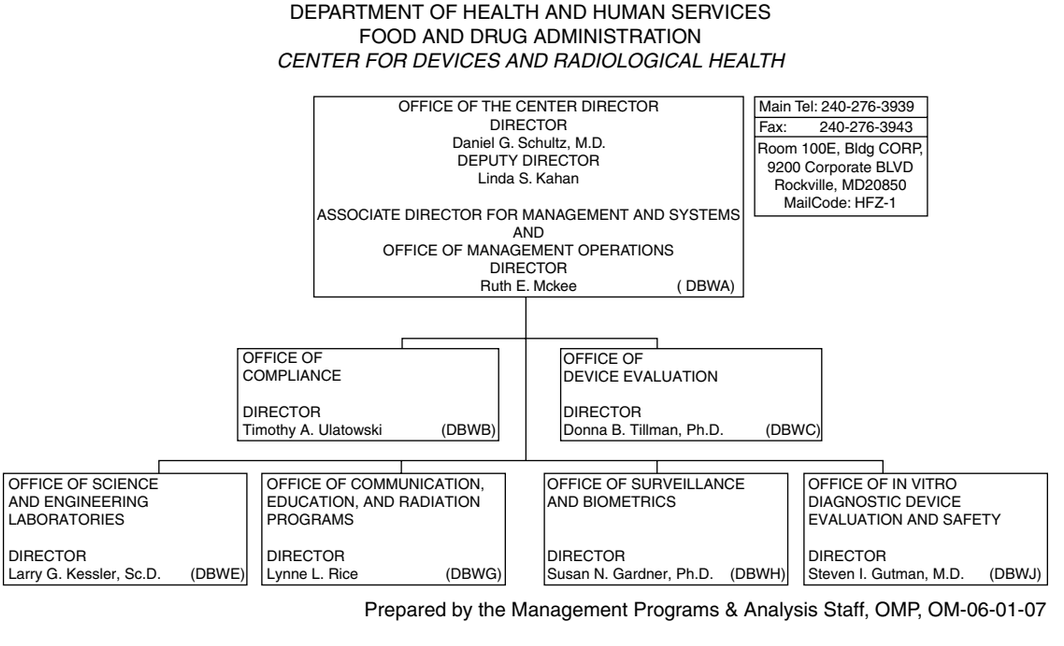

Figure 1.1 Organizational chart of the Office of Device Evaluation (ODE) for the Center for Devices and Radiological Health (CDRH) of the FDA. Current officials (as of 6/01/2007) are identified by name. ODE evaluates submissions for new device approvals. *Source:* http://www.fda.gov/oc/orgcharts/orgchart.html.

use for devices (such as general and restorative devices; cardiovascular, respiratory, and neurological devices; ophthalmic devices; reproductive, abdominal, ear, nose, and throat, and radiological devices; and clinical laboratory devices). Within each of these there are engineers, chemists, pharmacologists/toxicologists, statisticians, and clinicians.

There is also at least one nongovernmental body which must review and approve various aspects of devices, setting forth significant "guidance" for the evaluation of safety of devices. This is the USP, and its responsibilities and guidelines are presented later in Chapter 2.

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2

Regulatory Aspects and Strategy in Medical Device and Bio Materials Safety Evaluation

As discussed in Chapter 1, in the United States, according to 201(h) of the Food, Drug and Cosmetic Act, a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory that is:

(a) recognized in the official National Formulary, or the United States Pharmacopoeia (USP, 2007), or any supplement to them, and
(b) intended for use in the diagnosis of disease or other condition, 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 or man or other animals, and which does not achieve any of its primary 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 (CDRH, 1992).

REGULATORY BASIS

Regulations: General Considerations for United States

The U.S. regulations for medical devices derive from five principal laws:

Federal Food, Drug and Cosmetic Act of 1938
Medical Device Amendments of 1976
Safe Medical Devices Act of 1990
Medical Device Amendments of 1992
FDA Modernization Act of 1997 (Section 204).

The U.S. federal regulations that govern the testing, manufacture, and sale of medical devices are covered in Chapter 1, Title 21 of the Code of Federal Regulations (21 CFR). These comprise nine 6×8 inch volumes which stack 8 inches high. This title also covers foods, veterinary products, medical devices, and cosmetics. As these topics will be discussed elsewhere in this book, here we will briefly review those parts of 21 CFR that are applicable to medical devices (Gad, 2001; Heller, 1999).

Of most interest to a toxicologist working in this arena would be Chapter 1, Subchapter A (Parts 1–78), which cover general provisions, organization, etc. The good laboratory practices (GLPS) are codified in 21 CFR 58. The regulations applicable to medical devices are covered in Subchapter H, Parts 800–895 of 21 CFR. As discussed earlier, the term medical device covers a wide variety of products: contact lenses, hearing aids, intrauterine contraceptive devices, syringes, catheters, drip bags, orthopedic prostheses, etc. The current structure of the law was established by the Medical Device Amendment of 1976. Products on the market on the day the amendment was passed were assigned to one of three classes (I, II, or III), based on the recommendation of advisory panels. Medical device classification procedure is described in Part 860. Class I products (the least risk burdened) were those for which safety and effectiveness could be reasonably assured by general controls. Such devices are available over the counter to the general public. Class II products were those for which a combination of general controls and performance standards were required to reasonably assure safety and effectiveness. Class II devices are generally available only with a doctor's prescription, but may be used at home. Class III products were those for which general controls and performance standards were inadequate; these were required to go through a premarket approval process. All devices commercially distributed after May 28, 1976 ("preamendment Class III devices") which are not determined to be substantially equivalent to an existing marketed device are automatically categorized as Class III and require the submission of a PMA. Please note that these are classifications for regulatory purposes only and are distinct from the classification (HIMA/ PHRMA) of product types (e.g., internal *versus* external) discussed elsewhere in this chapter. Kahan (1995) provides a detailed overview of what comprises general controls, performance standards and such.

As with the subchapter on drugs, much of the subchapter on medical devices in the regulations concerns categorizations and specifics for a wide variety of devices. For a toxicologist involved in new product development, the parts of highest interest are 812 and 814. As with drugs, devices must be shown to be safe and effective when used as intended, and data must be provided to demonstrate such claims. In order to conduct the appropriate clinical research to obtain these data, a sponsor applies to the Agency for an IDE, as described in 21 CFR 812. As stated in this section, "an approved investigational device exemption (IDE) permits a device that would otherwise be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device." Given the broad range of products that fall under the category of medical devices, the toxicological concerns are equally broad; testing requirements to support an IDE are vaguely mentioned in the law, even by FDA standards. In this regard, the law simply requires that the IDE application must include a report of prior investigations which "shall include reports of all prior clinical, animal and laboratory testing." There is no absolute written requirement for animal testing, only a requirement that such testing must be reported.

There are, of course, standards and conventions to be followed in designing a safety package to support an IDE, and these are discussed in a subsequent section of this chapter.

The expansion and increased sophistication of ISO guidances has tended to shift the balance towards an increasing set of required pre-IDE biocompatibility tests.

In order to obtain a license to market a device, a sponsor either submits a 510(k) premarket notification or applies for a Premarket Approval (PMA), as described in 21 CFR 814. Like an NDA, a PMA application is a very extensive and detailed document that must include, among other things, a summary of clinical laboratory studies submitted in the application 921 CFR 814.20(b)(3)(v)(A), as well as a section containing results of the nonclinical laboratory studies with the device, including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. As with drugs, these tests must be conducted in compliance with the GLP Regulations. Under the language of the law, a sponsor submits a PMA, which the FDA then "files." The filing of an application means that "FDA has made a threshold determination that the application is sufficiently complete to permit substantive review." Reasons for refusal to file are listed in 814.44(e), and include items such as an application that is not complete and has insufficient justification for the omission(s) present. The agency has 45 days from receipt of an application to notify the sponsor as to whether or not the application has been filed. The FDA has 180 days after filing of a complete PMA (21 CFR 814,40) to send the applicant an approval order, an "approved" letter or a "not approved" letter, or an order denying approval. An "approval order" is self-explanatory and is issued if the agency finds no reason (as listed in 814.45) for denying approval. An "approved" letter 814.44(e) means the application substantially meets requirements, but some specific additional information is needed. A "not approved" letter, 814.45(f), means that the application contains false statements of fact, does not comply with labeling guidelines, or that nonclinical laboratory studies were not conducted according to GLPs, etc. Essentially, an order denying approval means that the sponsor must do substantially more work and must submit a new application for PMA for the device in question. 510(k) premarket approval submissions are less extensive than PMAs, but must still include appropriate preclinical safety data. 510(k)s are supposed to be approved in 90 days.

There is a third, little used route to move a new device to legal marketing approval in the U.S. This is the 513(f), filed for devices for which a 510(k) has been refused due to lack of a suitable predicate, but for which a determination of "no significant risk has been made."

Actual review and approval times historically have been much longer than the statutory limits. For 1995, the average total review time for Class III products in the United States cleared by 510(k) was 579 days (*versus* 240 or less in the EU) (The Gray Sheet, 1996a). For fiscal year 1996, overall average 510(k) review times (for an expected 5,875 filings) is projected to be 137 days (with low risk exempted devices and refusals to file not being included in the totals or average). Average PMA review times are projected to be 250 days (The Gray Sheet, 1996b). See Chapter 1 for a discussion of general regulatory considerations (such as Good Laboratory Practices) which are applicable to all safety evaluation studies.

Regulations Versus Law

A note of caution must be inserted here. The law (the document passed by Congress) and the regulations (the documents written by the regulatory authorities to enforce the laws) are separate documents. The sections in the law do not necessarily have numerical correspondence. For example, the regulations on the PMA process is described in 21 CFR 312, but the law describing the requirement for a PMA process is in Section 515 of the FDCA. Because the regulations rather than the laws themselves have a greater impact on the practice of nonclinical safety evaluation, greater emphasis is placed on regulation in this chapter. For a complete review of FDA law, the reader is referred to the monographs by Food and Drug Law Institute (FDLI) in 1995, 1996 and 1998.

FDA http://www.fda.gov/
CDER http://www.fda.gov/cder/
CBER http://www.fda.gov/cber/index.html

Organizations Regulating Device Safety in the United States

The agency formally charged with overseeing the safety of devices and diagnostics in the United States is the FDA. It is headed by a commissioner who reports to the Secretary of the Department of Health and Human Services (DHHS) and has a tremendous range of responsibilities. Medical devices are specifically overseen by the CDRH, headed by a director. Drugs are overseen primarily by the Center for Drug Evaluation and Research (CDER) (though some therapeutic or health care entities are considered as biologically derived and therefore regulated by the Center for Biologic Evaluation and Research, or CBER). There are also "combination products" (part drug, part device) which may be regulated by either or both CDER/CBER and CDRH, depending on what the principal mode of action (PMOA) is determined to be by the FDA (CFR, 1992), as discussed in Chapter 14.

Classification of Devices

In the United States, in accordance with the 1976 Medical Device Amendment, devices are categorized as below.

- Class I—General Controls (equivalent to OTC)
- Class II—Performance Standards and Special Controls (distribution is licensed healthcare professional controlled)
- Class III—Premarket Approval (clinical use only)
- Preamendment Devices.

In Europe, there is a lengthy set of rules in the EC Medical Device Directive (Council Directive, 1993) to place devices in Classes I, IIa, IIb or III. Class I is the minimum grade and Class II the maximum. This classification determines the extent of supporting data that is required to obtain marketing approval.

In the United States, the FDA Center for Devices and Radiological Health recognizes three classes of medical device, and this system is based on whether the product was on the market prior to the passage of the 1976 Medical Device Amendments. If a new device is substantially equivalent to a pre-amendment device, then it will be classified the same as that device. This means that for Class I and II products, no premarket approval is necessary. Class III products need pre-marketing approval, and all new devices which are not substantially equivalent to existing products fall automatically into Class III.

Japan (MHW) and Korea have a somewhat different three class system. Class I includes products that have no body contact and would not cause any damage to the human body if they failed, for example, x-ray film. These products need pre-marketing approval in terms of medical

device regulations, although they may need to be tested under industrial guidelines like those of the OECD. Class II products have external contact with the body, Class III have internal contact, and both need additional testing. Figure 2.1 presents the EFC scheme for device classification.

Most of the regulatory interaction of a toxicologist involved in assessing the biocompatibility of devices is with the appropriate part of the CDRH, though for combination products the two centers charged with drugs or biologicals may also come into play. Within the CDRH there is a range of groups (called divisions) which focus on specific areas of use for devices (such as general and restorative devices; cardiovascular, respiratory, and neurological devices; ophthalmic devices; reproductive, abdominal, ear, nose, and throat, and radiological devices; and clinical laboratory devices). Within each of these there are engineers, chemists, pharmacologists/toxicologists, statisticians, and clinicians.

There is also at least one nongovernmental body which must review and approve various aspects of devices, setting forth significant "guidance" for the evaluation of safety of devices. This is the USP, and its responsibilities and guidelines are presented later in this chapter.

The other two major regulatory organizations to be considered are the International Standards Organization (ISO), with ISO 10993 standards (ISO, various dates), and the Japanese Ministry of Health and Welfare (MHW) with its guidelines (MHW, 1995).

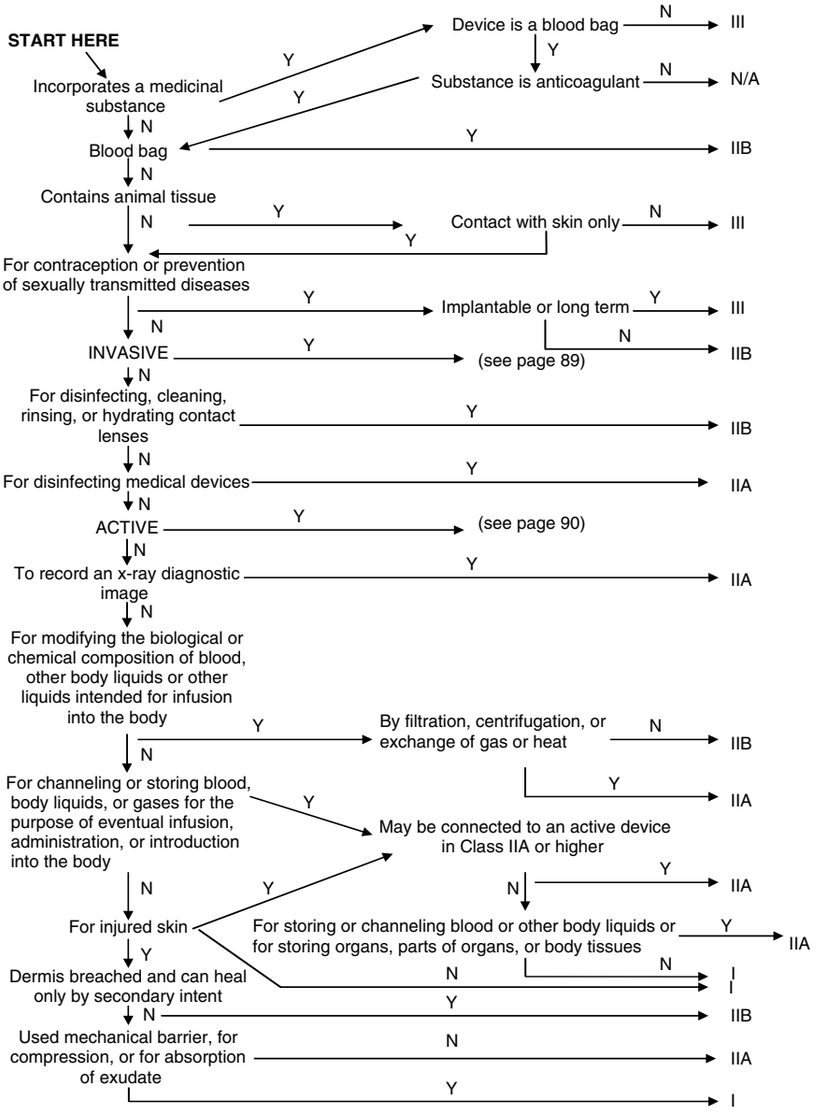

Figure 2.1 Medical device classification flowchart (*Continued*)

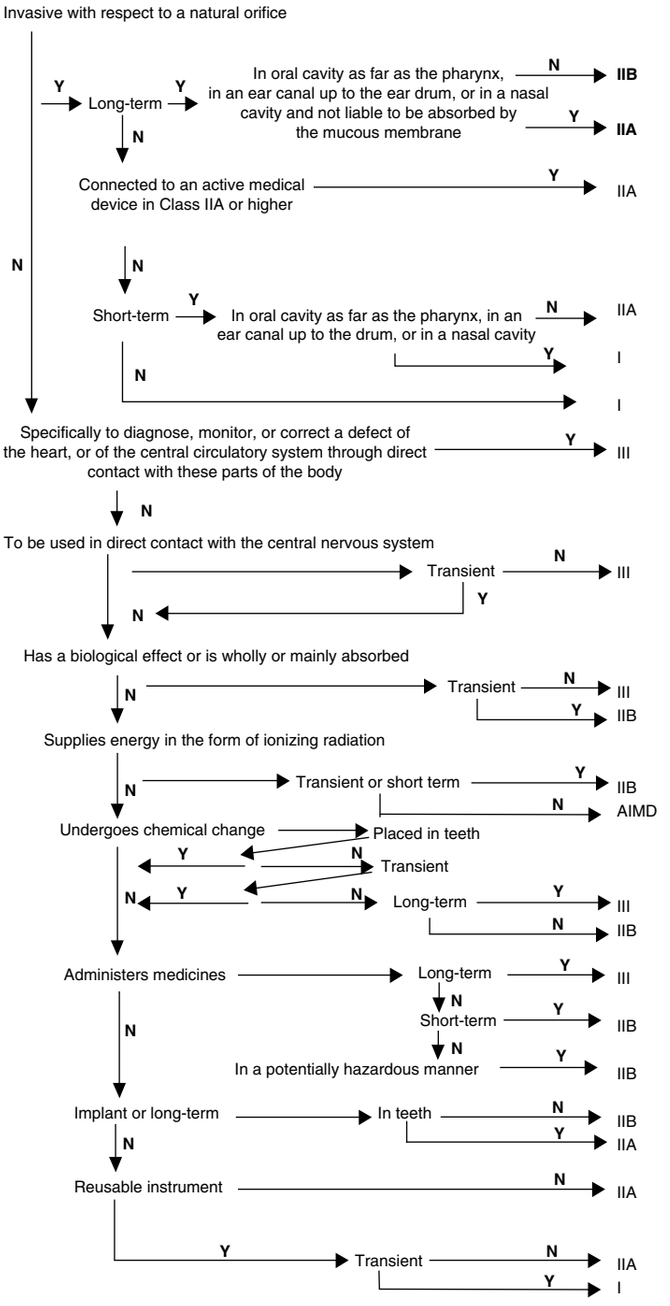

Figure 2.1 Continued

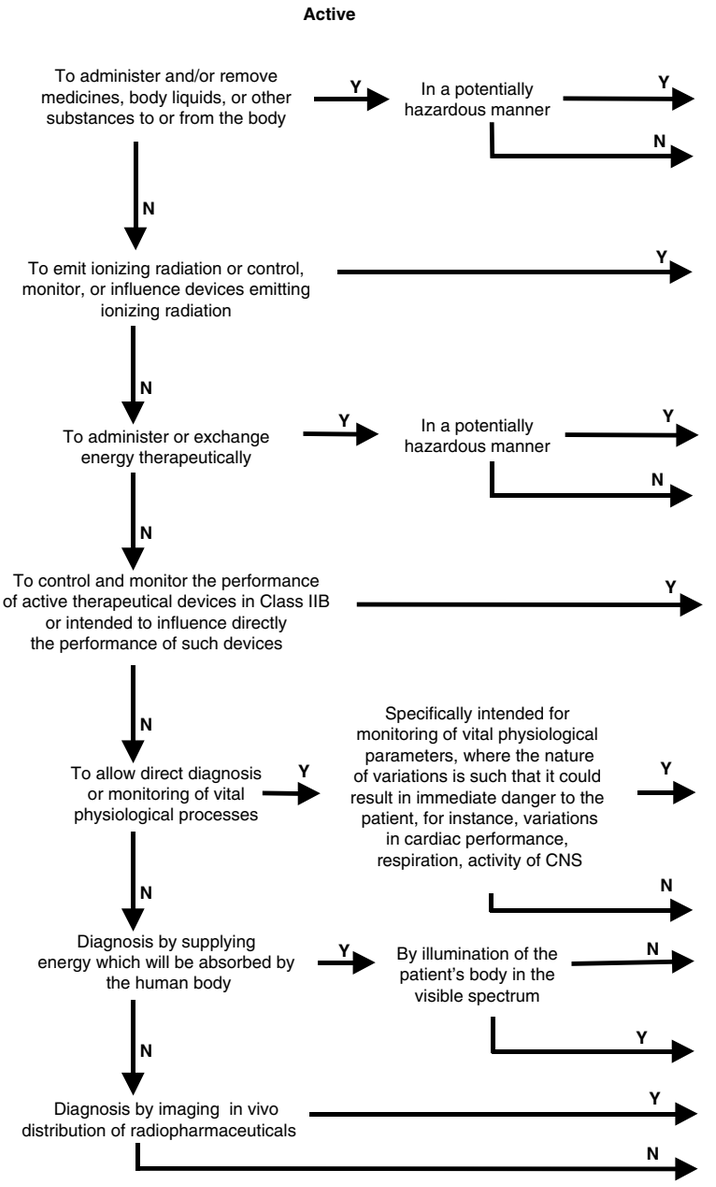

Figure 2.1 Continued

TOXICITY TESTING: MEDICAL DEVICES

In a statutory sense, any item promoted for a medical purpose which does not rely on chemical action to achieve its intended effect is a medical device (as discussed earlier). In vitro diagnostic tests are also regulated as medical devices. The regulation of devices under these definitions has had a different history than that of drugs—it has not been as strict and it has evolved at a slower rate. However, the requirements for the safety evaluation and biocompatibility evaluation of devices have rapidly been becoming more sophisticated and closer to that for new drugs. The safety concerns are, however, also somewhat different. Toxicologic safety concerns for devices (as opposed to concerns of mechanical safety, such as disintegration of heart valves) are called biocompatibility concerns.

Medical devices are classified as being in three different classes and are regulated accordingly. Class III devices are subject to the greatest degree of regulation and include devices which are implanted in the body, support life, prevent health impairment, or present an unreasonable risk of illness or injury. These are subject to premarketing approval. Class I and Class II devices are subject to lesser control, required only to comply with general controls and performance standards.

There are several governing schemes for dictating what testing must be done on new Class III devices in the general case, with each developed and proposed by a

different regulatory organization at different times over the last few years. ISO has attempted to harmonize these requirements so that different (or duplicate) testing would not need to be performed to gain device approval in different national markets. As discussed in the last chapter of this book, there are also specialized testing requirements for some device types such as contact lenses (CDRH, 1995a,b) and tampons (CDRH, 1995c). The ISO effort has generally been successful and parallels that of ICH for drugs (though ISO is, it should be noted, an NGO and not a governmental regulatory body. Where differences exist, they are highlighted in this volume as specific requirements and designs are presented.

As with drugs, all safety testing for devices must be conducted in conformity with GLPs (FDA, 1987; Fries, 1999; Gad and Taulbee, 1996). Table 2.1 presents the existing FDA CDRH requirements for device characterization and testing. The exact nature of the test protocols is based on recommendations by USP, ISO, and others. It should be noted that Class I devices, if new, are also subject to the ISO guidelines. It should also be noted that the FDA generally (but not strictly) now adheres to the ISO guidance on test requirements (Tables 2.12 and 2.13)

Additional concerns with devices are considerations of their processing after production. For example, concerns have risen about the potential for allergies to develop to latex components and for male reproductive effects for DEHP leaching from medical devices have led to the requirement that all such devices in either of these categories be appropriately labeled.

Devices which have systemic exposure need to be sterilized. Radiation and heat can be used for some devices, but others cannot be sterilized in these. Ethylene oxide or other chemical sterilants must be used, raising concerns that residual sterilants may present problems. At the same time, devices with exposure to the fluid path must be demonstrated to be neither pyrogenic nor hemolytic in their final manufactured form.

Table 2.1 FDA Device Categories and Suggested Biological Testing (FDA, 2000)

Device categories			Initial evaluation								Supplemental evaluation	
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute) pyrogonicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity
Surface devices	Skin	A	•	•	•							
		B	•	•	•							
		C	•	•	•							
	Mucosal membrane	A	•	•	•							
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
	Breached comprised surface	A	•	•	•	0						
		B	•	•	•	0	0	0				
		C	•	•	•	0	•	•	0		0	
External Communicating devices	Blood path indirect	A	•	•	•	•				•		
		B	•	•	•	•	0		•			
		C	•	•	0	•	•	•	0	•	•	•
	Tissue/bone dentin communicating	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		0	•
	Circulating blood	A	•	•	•	0						
		B	•	•	•	•	0	•	0	•		
		C	•	•	•	•	•	•	0	•	•	•
Implant devices	Bone/tissue	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•	•	•	•
	Blood	A	•	•	•	•			•	•		
		B	•	•	•	•	0	•	•	•		
		C	•	•	•	•	•	•	•	•	•	•

A = Limited exposure (≤ 24 hours) B = Prolonged exposure (24 hours – 30 days) C = Permanent contact (>30 days)

• = FDA and ISO evaluation tests 0 = Additional tests for FDA

[a] For these devices with possible leachables or degradation products, e.g., absorbable surfaces, hemostatic agents, etc., testing for pharmacokinetics may be required.

[b] Reproductive and developmental toxicity tests may be required for certain materials used for specialized indications.

[c] Considerations should be given to long-term biological tests where indicated in the table taking into account the nature and mobility of the ingredients in the materials used to fabricate the device.

1. The selection of material(s) to be used in device manufacture and its toxicological evaluation should initially take into account full characterization of the material, for example, formulation, known and suspected impurities, and processing.
2. The material(s) of manufacture, the final product, and possible leachable chemicals or degradation products should be considered for their relevance to the overall toxicological evaluation of the device.
3. Tests to be utilized in the toxicological evaluation should take into account the bioavailability of the bioactive material, i.e., nature, degree, frequency, duration, and conditions of exposure of the device to the body. This principle may lead to the categorization of devices which would facilitate the selection of appropriate tests.
4. Any in vitro or in vivo experiments or tests must be conducted according to recognized good laboratory practices followed by evaluation by competent informed persons.
5. Full experimental data, complete to the extent that an independent conclusion could be made, should be available to the reviewing authority, if required.
6. Any change in chemical composition, manufacturing process, physical configuration or intended use of the device must be evaluated with respect to possible changes in toxicological effects and the need for additional toxicity testing.
7. The toxicological evaluation performed in accordance with this guidance should be considered in conjunction with other information from other nonclinical tests, clinical studies, and postmarket experiences for an overall safety assessment.

Device Categories: Definitions and Examples

A. Noncontact Devices
   Devices that do not contact the patient's body directly or indirectly; examples include in vitro diagnostic devices.
B. External Devices
   1. *Intact surfaces* Devices that contact intact external body surfaces only; examples include electrodes, external prostheses, and monitors of various types.
   2. *Breached or compromised surfaces* Devices that contact breached or otherwise compromised external body surfaces; examples include ulcer, burn and granulation tissue dressings or healing devices, and occlusive patches.
C. Externally Communicating Devices
   1. *Intact natural channels* Devices communicating with intact natural channels; examples include contact lenses, urinary catheters, intravaginal and intraintestinal devices (sigmoidoscopes, colonoscopes, stomach tubes, gastroscopes), endotracheal tubes, and bronchoscopes.
   2. *Bloodpath, indirect* Devices that contact the blood path at one point and serve as a conduit for fluid entry into the vascular system; examples include solution administration sets, extension sets, transfer sets, and blood administration sets.
   3. *Blood path, direct* Devices that contact recirculating blood; examples include intravenous catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, and dialyzers, dialysis tubing and accessories.
D. Internal Devices
   1. *Bone* Devices principally contacting bone; examples include orthopedic pins, plates, replacement joints, bone prostheses and cements.
   2. *Tissue and tissue fluid* Devices principally contacting tissue and tissue fluid or mucus membranes where contact is prolonged; examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, cerebrospinal fluid drains, artificial larynx, vas deferens valves, ligation clips, tubal occlusion devices for female sterilization, and intrauterine devices.
   3. *Blood* Devices principally contacting blood; examples include permanent pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, blood monitors, internal drug delivery catheters, and ventricular assist pumps.

Biological Tests

Also required to properly utilize the tables is a knowledge of the objectives of the specified biological tests. These can be considered as follows (Gad and Chengelis, 1998; Goering and Galloway, 1989):

Sensitization Assay Estimates the potential for sensitization of a test material and/or the extracts of a material using it in an animal and/or human. ISO (ISO, 1992, 1996) and MHW procedures are contrasted in Table 2.2.

Irritation Tests Estimates the irritation potential of test materials and their extracts, using appropriate site or implant tissue such as skin and mucous membrane in an animal model and/or human. ISO and MHW procedures are contrasted in Table 2.3; and for eye irritation in Table 2.4.

Cytotoxicity With the use of cell culture techniques, this test determines the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by test materials and/or extracts from the materials. ISO and MHW procedures are contrasted in Table 2.5.

Acute Systemic Toxicity Estimates the harmful effects of either single or multiple exposures to test materials and/or extracts, in an animal model, during a period of less than 24 hours. ISO and MHW procedures are contrasted in Table 2.6.

Hematocompatibility Evaluates any effects of blood contacting materials on hemolysis, thrombosis, plasma-proteins, enzymes, and the formed elements using

Table 2.2 Differences Between Sensitization Test Procedures Required by ISO 10993-10 and the MHW Guidelines

ISO 10993-10	MHW 1995
Sample preparation:	
Extraction in polar and/or nonpolar solvents.	Two extraction solvents, methanol and acetone, recommended.
Extraction ratio:	
Extraction ratio is dependent on thickness of device or representative portion.	Specific extraction ratios: 10:1 (volume solvent:weight sample)
Extract used for testing.	
If extraction is not possible, the adjuvant and patch test can be utilized.	Residue obtained from extraction is redissolved and used for testing. (If residue does not dissolve in DMSO, or a sufficient amount of residue is not obtained, the adjuvant and patch test is recommended). Sufficient amount of residue: 0.1–0.5% (weight residue:weight test material)

Table 2.3 Differences in Intracutaneous Reactivity Test Procedures Required by ISO 10993-10 and the MHW Guidelines

ISO 10993-10	MHW
Number of test animals:	
Three rabbits for 1 to 2 extracts.	Two rabbits for each extract.
Number of test/control injections per extract:	
Five test and five control injections.	Ten test and five control injections.
Evaluation of responses:	
Quantitative comparison of responses of test and control responses.	Qualitative comparison of test and control responses.

an animal model. Traditionally, hemolysis, which determines the degree of red blood cell lysis and the separation of hemoglobin caused by test materials and/or extracts from the materials in vitro, has been "the" representative test employed. A broader range of primary tests (adding evaluations of thrombosis, coagulation, platelets, and immunology aspects) is currently recommended. ISO and MHW procedures for hemolysis are contrasted in Table 2.7.

Implantation Tests Evaluates the local toxic effects on living tissue, at both the gross level and microscopic level, to a sample material that is surgically implanted into appropriate animal implant site or tissue, e.g., muscle, bone; for 7–90 days. ISO and MHW procedures are contrasted in Table 2.10.

Mutagenicity (Genotoxicity) The application of mammalian or non-mammalian cell culture techniques for the determination of gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by test materials and/or extracts from materials. Selected tests representing gene mutation tests (Ames or mouse lymphoma), chromosomal aberration tests (CHO) and DNA effects tests (mouse micronucleous and sister chromatid exchange) should generally be employed. ISO and MHW procedures are contrasted in Table 2.10.

Subchronic Toxicity The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of one day to less than 10% of the total life of the test animal (e.g., up to 90 days in rats).

Chronic Toxicity The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of 10% to the total life of the test animal (e.g., over 90 days in rats).

Carcinogenesis Bioassay The determination of the tumorigenic potential of test materials and/or extracts from either single or multiple exposures, over a period of the total life (e.g., 2 years for rat, 18 months for mouse, or 7 years for dog).

Pharmacokinetics To determine the metabolic processes of absorption, distribution, biotransformation, and elimination of toxic leachables and degradation products of test materials and/or extracts.

Reproductive and Developmental Toxicity The evaluation of the potential effects of test materials and/or extracts on fertility, reproductive function, and prenatal and early postnatal development.

Table 2.4 Differences in Eye Irritation Testing Procedures Outlined in ISO 10993-10 and the MHW Guidelines

ISO 10993-10	MHW 1995
Time of exposure:	
1 second	Thirty seconds
Grading scale:	
Classification system for grading ocular lesions	Draize or McDonald–Shadduck scale.

Table 2.5 Differences Between Cytotoxicity Test Procedures Specified by ISO 10993-5 and the MHW Guidelines (MHW, 1995)

ISO 10993-10	MHW 1995
Number of cells per dish:	
0.5–1 million cells	40 to 200 cells per dish
Extraction ratio:	
60 cm^2 per 20 mL if thickness 80.5 mm 120 cm^2 per 20 mL if thickness 70.5 mm or 4g per 20 mL	5 cm^2/mL or 1 g/10 mL
Exposure period:	
Typically 24–72 hours (2 hours for filter diffusion test)	6–7 days
Toxicity determination:	
Visual grading and/or quantitative assessments	Quantification of surviving colonies
Positive controls:	
Materials providing a reproducible cytotoxic response (e.g., organo-tin-impregnated polyvinyl chloride)	Segmented polyurethane films containing 0.1% zinc diethyldithiocarbamate and 0.25% zinc dibutyldithiocarbamate

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. Chapter 3 addresses the issues behind sampling, sample preparation, and solvents.

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. Table 2.10 presents the basis for test selection under the Tripartite Agreement.

United States Pharmacopoeial Testing

The earliest guidance on what testing was to be done on medical devices was that provided in the USP and other pharmacopoeias. Each of the major national pharmacopoeias offers somewhat different guidance. The test selection system for the USP (presented in Table 2.10), which classified plastics as Classes I through VI, is now obsolete and replaced in usage by the other guidelines presented here. But the actual descriptions of test types, as provided in the USP (and presented in the appropriate chapters later in this book) are still very much operative (USP, 1994).

There are British, European, and Japanese pharmacopoeias, of which the latter requires the most attention due to some special requirements still being operative if product approval is desired.

ISO Testing Requirements

The European Economic Community has adopted a new set of testing guidelines for medical devices under the aegis of

Table 2.6 Comparison of Grading Scales Used to Score Responses of Test Animals to ASTM and ISO/USP Procedures

Response	ASTM Description	ISO/USP
Normal, no symptoms	Mouse exhibits no adverse physical symptoms after injection.	
Slight	Mouse exhibits slight but noticeable symptoms of hypokinesis, dyspnea, or abdominal irritation after injection.	
Moderate	Mouse exhibits definite evidence of abdominal irritation, dyspnea, hypokinesis, ptosis, or diarrhea after injection. (Weight usually drops to between 15 and 17 g.)	
Marked	Mouse exhibits prostration, cyanosis, tremors, or severe symptoms of abdominal irritation, diarrhea, ptosis, or dyspnea after injection. (Extreme weight loss; weight usually less than 15 g.)	
Dead, expired	Mouse dies after injection.	
	Interpretation	*Interpretation*
	The test is considered negative if none of the animals injected with the test article extracts shows a significantly greater biological reaction than the animals treated with the control article.	The test is considered negative if none of the animals injected with the test article shows a significantly greater biological reaction than the animals treated with the control article.
	If two or more mice show either marked signs of toxicity or die, the test article does not meet the requirements of the test.	If two or more mice die, or show signs of toxicity such as convulsions or prostration, or if three or more mice lose more than 2 g of body weight, the test article does not meet the requirements of the test.
	If any animal treated with a test article shows slight signs of toxicity, and not more than one animal shows marked signs of toxicity or dies, a repeat test using freshly prepared extract should be conducted using groups of 10 mice each. A substantial decrease in body weight for all animals in the group, even without other symptoms of toxicity, requires a retest using groups of 10 mice each. In the repeat test, the requirements are met if none of the animals injected with the test article shows a substantially greater reaction than that observed in the animals treated with the control article.	If any animal treated with a test article shows only slight signs of biological reaction, and not more than one animal shows gross signs of biological reaction or dies, a repeat test should be conducted using groups of 10 mice. On the repeat test, all 10 animals must not show a significantly greater biological reaction than the animals treated with the control article.

ISO (ISO, 1992; The Gray Sheet, 1992). The ISO 10993 guidelines for testing provide a unified basis for international medical device biocompatibility evaluation, both in terms of test selection (as presented in Tables 2.11 and 2.12) and test design and interpretation (Table 2.13). In 1996, the United States FDA also announced that it would adhere to ISO 10993 standards for device biocompatibility evaluation.

This international standard specifies methods of biological testing of medical and dental materials and devices and their evaluation in regard to their biocompatibility. Because of the many materials and devices used in these areas, the standard offers a guide for biological testing.

MHW Requirements

The Japanese ISO test selection guidelines vary from those of FDA and ISO and are summarized in Table 2.15 (MHW, 1995; *Japanese Pharmacopoeia*, 1996).

Table 2.7 Differences in Hemolysis Test Procedures Recommended by ISO 10993-4 and the MHW Guidelines

ISO 10993-4	MHW 1995
Hemolysis can be assessed by any of several validated methods to assay hemoglobin in plasma.	Hemolytic index is assessed by measuring hemoglobin at 1, 2, and 4 hours by spectrophotometric methods. The hemolysis over this period is expressed as a percentage of the positive control.

Actual test performance standards also vary, as shown in Tables 2.3–2.10.

Committees dealing with materials and devices must decide on tests and test series relevant to the respective materials and devices, It is the responsibility of the product committees to select adequate test methods for products. The standard contains animal tests, but tries to reduce those tests to the justifiable minimum. Relevant international and national regulations must be observed when animals are used.

Table 2.8 Comparison of Pyrogen Test Procedures Required by ISO 10993-11 and the MHW Guidelines

ISO 10993-11	MHW 1995
Number of animals:	
Three rabbits required; comparison of febrile response in test animals to baseline temperature for evaluation of pyrogenicity potential	Three rabbits (test) required; comparison to baseline temperature is evaluated as index of pyrogenicity potential
Test duration:	
Test measurement intervals: every 30 minutes for 3 hours	Test measurement intervals: every hour for 3 hours
Evaluation:	
Cutoff for positive febrile response: 0.5°C	Cutoff for positive febrile response: 0.6°C

Table 2.9 Differences in ISO 10993-3 and the MHW Guidelines for Assessing the Effects of Device or Material Implantation

ISO 10993-3	MHW 1995
Time point(s) of assessment:	
Sufficient to achieve steady state (e.g. 2, 4, 6, and 12 weeks)	7 days and 4 weeks
Number of animals:	
At least three per time period of assessment	At least four per time period
Number of samples of evaluation:	
At least eight per time period for test and control	No minimum number specified
Evaluation criteria:	
Comparative evaluation of responses to test and control materials	If more than two of the four test sites in each animal exhibit a significant response compared to control sites, the test is considered positive

ISO 10993 is based on existing national and international specifications, regulations, and standards wherever possible. It is open to regular review whenever new research work is presented to improve the state of scientific knowledge. Tables 2.3 and 2.4 provide the test matrices under ISO 10993. Subsequently, specific guidance on individual test designs, conduct and interpretation has been provided as subparts 2-11 of ISO-10993 (Table 2.13) (AAMI, 2006).

CE Marking of Devices

After June 14, 1998, all medical products distributed in Europe have had to bear the CE mark. ISO 9000 certification supplements and supports an assessment of conformity to the Medical Devices Directive (MDD), which must be performed by a certification body appointed by the EU member states (Haindl, 1997). To qualify for the CE mark, manufacturers of Class IIa, IIb, and III devices must be certified by a notified body (which is recognized by the national health authorities) to Annex II, V, or VI of the MDD (also known as 93/42/EEC) and comply with the essential requirements of the directive. Manufacturers of active implantables and IVDs have separate directives to contend with. When auditing for compliance, the notified body will check a number of items in addition to a manufacturer's QA system, including technical files, sterility assurance measures, subcontracting procedures, recall and vigilance systems, and declarations of conformity. Depending on the classification and certification route, some devices will also require an EC-type examination or a design review by the notified body.

Manufacturers of Class I products, who require minimal interaction with a notified body, appear to be the clear winners in this scheme, but even they must deal with a number of vague or confusing requirements (Table 2.15). Simply classifying their products according to the dictates of 93/42/EEC, Annex IX, can be a tricky affair, and faulty classification can lead to bigger problems. The simplified flowcharts in Figure 2.1 should help manufacturers determine whether their products qualify as Class I devices. For more difficult products, manufacturers may need to refer to a consultant or obtain a suitable software program.

Classification is based on the intended and declared use of a product, not solely on its salient features. The Class I designation usually—but not always—excludes sterile products and measuring devices that measure physiological parameters or require a high degree of accuracy. So, for example, a reusable scalpel is Class I, but a sterile scalpel is Class IIa; a scalpel blade for the reusable device is Class I, but if it is supplied sterile, it is Class IIa; a scalpel blade for the reusable device is Class I but if it is supplied sterile, it is Class IIa. A stethoscope, a simple graduated syringe (not for injection pumps), and a measuring spoon for administering an expectorant are not considered measuring devices, although a hand-driven blood-pressure gage and a digital thermometer are.

All of the classification rules are included in the directive, but they are not easy to understand. An EC working group has drawn up a separate paper known as MEDDEV 10/93 to explain the rules and provide some practical guidelines. For example, the directive stipulates that reusable surgical instruments belong in the Class I designation as long as they are not intended for more than an hour of continuous use. According to this definition, items such as scissors and tweezers, even if they are used in a six-hour operation, are still considered Class I devices because they are not used continuously during that time.

Even if a Class I product is supplied sterile, the manufacturer must issue a self-declaration of conformity. In this case, the manufacturer need only certify the QC system governing those aspects of manufacture concerned with securing and maintaining sterile conditions. If the device is packaged and sterilized by a company that works with a certified process, then the manufacturer must only validate the process for the particular device and submit the results to

Table 2.10 Differences in Genotoxicity Testing Procedures Required by ISO 10993-3 and the MHW Guidelines

ISO 10993-10	MHW 1995
Extraction vehicles:	
A physiological medium is used and, where appropriate, a solvent (e.g., dimethylsulfoxide)	Recommends methanol and acetone as extracting vehicles
Extraction:	
Extract test material and test the extract or dissolve material in solvent and conduct test. The conditions of extraction should maximize the amount of extractable substances, as well as subject the test device or material to the extreme conditions it may be exposed to, without causing significant degradation. Extraction ratio is dependent on thickness of test material.	Extract at room temperature at a ration of 10:1 (solvent:material) and obtain residue (at least 0.1–0.5% [weight of residue/weight of test material]), redissolve in appropriate solvent and test residue. If sufficient residue is unobtainable, extract test material (in ethanol, acetone, or DMSO at 10 g of test material per 20 mL for the Arnes mutagenicity assay, and in cell culture medium at 120 cm^3 or 4 g/20 mL for the chromosomal aberration assay), at 37°C for 48 hours and test extract. The Ames mutagenicity assay is conducted with a volume of 200 μL per plate.

Table 2.11 Classification of Plastics (USP XXIII)

Plastic classes[a]						Tests to be conducted			
I	II	III	IV	V	VI	Test material	Animal	Dose	Procedures[b]
x	x	x	x	x	x	Extract of sample in sodium chloride inspection	Mouse	50 mL/kg	A (iv)
x	x	x	x	x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
x	x	x	x	x		Extract of sample in 1 in 20	Mouse	50 mL/kg	A (iv)
x	x	x	x	x		Solution of alcohol in sodium chloride injection	Rabbit	0.2 mL/animal at each of 10 sites	
	x		x	x		Extract of sample in polyethylene glycol 400	Mouse	10 g/kg	A (ip)
		x	x				Rabbit	0.2 mL/animal at each of 10 sites	
		x	x	x	x	Extract of sample in vegetable oil	Mouse	50 mL/kg	A (ip)
			x	x	x		Rabbit	0.2 mL/animal at each of 10 sites	B
		x			x	Implant strips of sample	Rabbit	4 strips/animal	C

[a]Tests required for each class are indicated by "x" in appropriate rows.

[b]*Legend*: A (ip), Systemic injection test (intraperitoneal); A(iv), Systemic injection test (intravenous); B, Intracutaneous (Intracutaneous); C, Implantation test (intramuscular implantation).

The table lists the biological tests that might be applied in evaluating the safety of medical devices and/or polymers. This does not imply that all the tests listed under each category will be necessary or relevant in all cases. Tests for devices made of metals, ceramics, biological materials, etc., are not included here but are under consideration.

Categorization of medical devices is based on body contact and contact duration.

Table 2.12 ISO Initial Evaluation Tests

Device categories		Biological tests								
Body contact duration A—limited exposure B—prolonged or repeated exposure C—permanent contact		Cytotoxicity	Sensitization	Irritation or intracutaneous	Acute systemic toxicity	Subchronic toxicity	Mutagenicity	Pyrogenicity	Implantation	Hemocompatability
Surface devices:										
	A	x	x	x						
Skin	B	x	x	x						
	C	x	x	x						
	A	x	x	x						
Mucous membranes	B	x	x	x						
	C	x	x	x		x	x			
	A	x	x	x						
Breached surface	B	x	x	x						
	C	x	x	x		x	x			
Externally communicating:										
	A	x	x	x				x		x
Blood path indirect	B	x	x	x				x		x
	C	x	x		x	x	x	x		x
	A	x	x	x						
Tissue/bone communicating	B	x	x				x		x	
	C	x	x				x		x	
Internal devices:										
	A	x	x	x	x			x		x
Circulating blood	B	x	x	x	x		x	x		x
	C	x	x	x	x	x	x	x		x
Implant devices:										
	A	x	x	x						
Bone/tissue	B	x	x				x		x	
	C	x	x				x		x	
	A	x	x	x	x			x	x	x
Blood	B	x	x	x	x		x	x	x	x
	C	x	x	x	x	x	x	x	x	x

a notified body. The manufacturer still needs certification by a notified body in regard to the performance aspects relating to sterility and measurement function; the notified body will also want to inspect the manufacturer's facility. Nonetheless, the procedure is far less complicated than a full production audit.

All manufacturers applying for CE marking privileges—including manufacturers of Class I devices—must prepare the proper technical documentation; appoint a "responsible person" within the EEC; design product labels and labeling according to 93/42/EEC, Annex I, paragraph 13; and sign a declaration of conformity. The technical dossier should not pose a major problem for manufacturers familiar with device master files. A list of required dossier contents is given in Table 2.16. For biological material testing, Europe uses the ISO 10993 (EN 30993) protocols, but test results according to the Tripartite agreement (or USP XXIII) are accepted. Every electrical device must also be proven to comply with the EMC requirements defined in the MDD; suppliers of preassembled electrical components may have the appropriate test results already available. Reformatting an existing device master file is not necessary, only creating an index that cross-references the essential requirements of the directives with the device file contents. The master file is a controlled document, as defined in ISO 9000, and manufacturers would do well to regard it as highly confidential.

The technical dossier is closely linked to the responsible person, a representative in the EEC governed by European law and authorized by the manufacturer to oversee routine regulatory affairs. Specifically, the responsible person must ensure compliance with the European vigilance system, which covers both postmarket surveillance and adverse-incident reporting. For example, if a patient were injured by a device, or if a patient would have been injured had the caregiver not intervened, the responsible person would have to investigate the incident together with the device's manufacturer and file a report with the competent authorities. Moreover, the European authorities must be able to obtain the master file in case of trouble; therefore, the manufacturer must either store the file or its abbreviated form with the responsible person or draw up a contractual agreement that gives the agent the right to access the master file without delay if required by the authorities. The agent must be available all year, as the time frame for notification could be as

Table 2.13 ISO Special Evaluation Tests

Device categories		Biological tests			
Body contact duration A—limited exposure B—prolonged or repeated exposure C—permanent contact (time limits to added)		Chronic toxicity	Carcinogenicity	Reproductive/developmental	Degradation
Surface devices:					
	A				
Skin	B				
	C				
	A				
Mucous membranes	B				
	C				
	A				
Breached surface	B				
	C				
Externally communicating:					
	A				
Blood path indirect	B				
	C	x	x		
	A				
Tissue/bone communicating	B				
	C		x		
Internal devices:					
	A				
Circulating blood	B				
	C	x	x		
	A				
Bone/tissue	B				
	C	x	x		
	A				
Blood	B				
	C	x	X		

Table 2.14 ANSI/AAMI/ISO Standards

	ISO designations	Year issued
Evaluation and testing	10993-1	2003
Animal welfare requirements	10993-2	2006
Tests for genotoxicity, carcinogenicity and reproductive toxicity	10993-3	2003
Selection of tests for interactions with blood	10993-4	2002 and A1/2006
Tests for *in vitro* cytotoxicity	10993-5	1999
Tests for local effects after implantation	10993-6	1995/(R)2001
Tests for irritation and delayed-type hypersensitivity	BE78	2002
Ethylene oxide sterilization residuals	10993-7	1995/(R)2001
CANCELLED	10993-8	—
Framework for identification and quantification of potential degradation products	10993-9	1999/(R)2005
Tests for systemic toxicity	10993-11	2006
Sample preparation and reference materials	10993-12	2002
Identification and quantification of degradation products from polymeric devices	10993-13	1999/(R)2004
Identification and quantification of degradation products from ceramics	10993-14	2001
Identification and quantification of degradation products from metals and alloys	10993-15	2000
Toxicokinetic study design for degradation products and leachables from medical devices	10993-16	1997/(R)2003
Establishment of allowable limits for leachable substances	10993-17	2002
Physio-chemica, morphological and topographical characterization of materials	10993-19	2006
Chemical characterization of materials	BE83	2006
Principles and methods for immunotoxicology testing of medical devices	10993-20	2006
Clinical Investigation of medical devices for human subjects-Part 1: General requirements	14155-1	2003
Clinical Investigation of medical devices for human subjects—Part 2: Clinical Investigation plans	14155-2	2003

Table 2.15 Japanese MHW Test Selection Guidelines

Device categories			Initial evaluation								Supplemental evaluation		
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute) pyrogonicity	Subchronic toxicity	Genotoxicity	Pyrogen	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity
Surface devices	Skin	A	X	X	X								
		B	X	X	X								
		C	X	X	X								
	Mucosal membrane	A	X	X	X								
		B	X	X	X								
		C	X	X	X		X	X					
	Breached/compromised surface	A	X	X	X								
		B	X	X	X								
		C	X	X	X		X	X					
External Communicating devices	Blood path indirect	A	X	X	X	X			X		X		
		B	X	X	X	X			X		X		
		C	X	X		X	X	X	X		X	X	X
	Tissue/bone dentin communicating	A	X	X	X								
		B	X	X				X		X			
		C	X	X				X		X			X
	Circulating blood	A	X	X	X	X			X		X		
		B	X	X	X	X		X	X		X		
		C	X	X	X	X	X	X	X		X	X	X
Implant devices	Bone/tissue	A	X	X	X								
		B	X	X				X		X			
		C	X	X				X		X		X	X
	Blood	A	X	X	X	X			X	X	X		
		B	X	X	X	X		X	X	X	X		
		C	X	X	X	X	X	X	X	X	X	X	X

A = Temporary contact (<24 hours) B = Short- and medium-term contact (24 hours–29 days) C = Long-term contact (>30 days)

short as 10 days. Ideally, the responsible person should be familiar with the national regulation in all member states.

The simplest way to maintain a European address will be to appoint a distributor as their responsible person, although this course is not without potential problems. The selected distributor does not need certification as long as the manufacturer's name and CE mark are on the product labeling. The name of the responsible person must also appear on the label, package insert, or outer packaging, even if the product is sold by a completely different distributor in another country. There is no official rule or proposal regarding how many responsible persons a manufacturer should have, but each one must appear on the labeling; therefore, appointing more than one is of limited use. The responsible person should be selected with great care; device master files (Table 2.16) must be made available to the responsible person in the event of patient injury or near injury, and many distributors are potential competitors. Class I devices, by nature, will rarely lead to patient injury, but manufacturers should still consider labeling issues when choosing a representative. It is easy to change distributors, but changing the responsible person means changing all the product labeling.

Table 2.16 Which Products are Class I?

The classification of a product refers to its intended use. The following is a simplified listing of Class I products:

- Noninvasive (and nonactive) devices that do not modify the biological or chemical composition of blood or liquids intended for infusion; store blood, body liquids, or tissues for administration; or connect to an active medical device.
- Dressings intended only as a mechanical barrier or for absorption of exudates.
- Invasive products for use in natural body orifices and stomas for no longer than one hour or in the oral or nasal cavity or ear canal for up to 30 days.
- Surgical invasive products if they are reusable instruments and not intended for continuous use of more than one hour.
- Active devices that administer neither energy nor substances to the body nor are made for diagnosis.

Class I products cannot:

- Incorporate medicinal products (drugs) or animal tissue.
- Be intended for contraception or the prevention of sexually transmitted diseases.

As an alternative, manufacturers can contract with a professional agency to serve as a representative completely independent from any distribution network.

The issue of labeling is itself a source of contention. Not all countries have decided yet whether they will insist on having their own language on device labels. Many countries have rather imprecise rules, dictating that their national language must appear only if necessary. Manufacturers can reduce potential trouble by using the pictograms and symbols defined in the harmonized European standard EN 980. For instructions of use, manufacturers are advised to use all 12 languages used in the European Economic Area. The requirements for labeling are presented in Annex I, paragraph 13, of the MDD; some devices may be subject to additional requirements outlined in product standards.

Class I products fall under the jurisdiction of local authorities, but who serves as those authorities may differ from country to country. In Germany, for example, there are no clear-cut regulations that define the competence of the local authorities, except in the case of danger to the patient. European product liability laws more or less give the consumer the right to sue anybody in the trade chain. Normally, claims would be filed against the manufacturer, but it is possible that there will be claims against a responsible person. This is a rather new legal situation, and the rules will be determined by court decisions. It is hoped that Class I products will not instigate many court actions, but clearly, even manufacturers of Class I devices will have a host of new concerns under the CE marking scheme.

Table 2.17 Contents of a Device Master File

1. EC declaration of conformity and classification according to Annex IX of the MDD.
2. Name and address of the manufacturer's European responsible person.
3. Product description, including:
   - All variants.
   - Intended clinical use.
   - Indications/contraindications.
   - Operating instructions/instructions for use.
   - Warnings/precautions.
   - Photographs highlighting the product.
   - Photographs highlighting the usage.
   - Brochures, advertising, catalog sheets, marketing claims (if available).
   - Product specifications including:
   - Parts list, list of components.
   - Specifications of materials used, including data sheets.
   - List of standards applied.
   - Details of substance(s) used (in the event of drug-device combination).
   - QA specifications (QC specs, in-process controls, etc) etc.
   - Labeling, accompanying documents, package inserts (DIN EN 289, prEN 980).
   - Instruction for use (prEN 1041).
   - Service manual.
   - Product verification, including:
   - Testing data and reports, functionality studies, wet lab or benchtop testing.
   - Materials certificates/reports on biological tests.
   - EMC testing and certificates.
   - Validation of the packaging/aging studies.
   - Compatibility studies (connection to other devices).
   - Risk analysis (DIN EN 1441).
   - Clinical experience.
4. List of requirements (Annex I) indicating cross-reference with documentation.

Risk Assessment

The reality is that not all materials used on devices are entirely safe. Generally, if one looks long enough at small enough quantities, some type of risk can be associated with every material. Risk can be defined as the possibility of harm or loss. Health risk, of course, is the possibility of an adverse effect on one's health. Risk is sometimes quantified by multiplying the severity of an event times the probability the event will occur, so that:

$$\text{Risk} = \text{severity} \times \text{probability}$$

While this equation appears useful in theory, in practice it is difficult to apply to the biological safety of medical devices. The process known as health-based risk assessment attempts to provide an alternative strategy for placing health risks in perspective (Stark, 1998; AAMI, 1998).

Standards and Guidances

A paradigm for the risk assessment process has been detailed in a publication prepared by the U.S. National Academy of Sciences (Hayes, 1994). Although devised primarily for cancer risk assessment, many of the provisions also apply to the assessment of other health effects. The major components of the paradigm are (1) hazard identification, (2) dosage-response assessment, (3) exposure assessment, and (4) risk characterization (Ecobichon, 1992).

The general approach to risk assessment was adapted to medical devices via the draft CEN standard *Risk Analysis*, published in 1993,[a] and more recently via the ISO standard, *ISO 14538—Method for the establishment of Allowable Limits for Residues in Medical Devices Using Health-Based Risk Assessment*, published in 1996.[b] At the present time, the FDA is also working to develop a health-based risk assessment protocol adapted to medical devices. Informally called the Medical Device Paradigm, the document is not yet generally available (Brown and Stratmeyer, 1997).[c]

Some manufacturers may object that regulators are once again attempting to impose a "drug model" on medical devices. However, we shall see in the following pages that judicious application of these risk assessment principles can provide a justification for using materials that carry with them some element of risk, and that may, under traditional biocompatibility testing regimes, be difficult to evaluate or be deemed unsuitable for medical device applications.

Method

Hazard Identification

The first step in the risk assessment process is to identify the possible hazards that may be presented by a material. This is accomplished by determining whether a compound, an extract of the material, or the material itself produces adverse effects, and by identifying the nature of

[a] *CEN BTS 3/WG 1—Risk Analysis* is available through the British Standards Institute.

[b] Available from the Association for the Advancement of Medical Instrumentation, 3330 Washington Blvd., Ste. 400, Arlington, VA 22201, USA.

[c] Draft copies of the Medical Device Paradigm may be obtained by contacting Dr. Melvin Stratmeyer, FDA Center for Devices and Radiological Health, HFZ-112, Division of Life Sciences, Office of Science and Technology, FDA, Rockville, MD 20857, USA.