Chapter 1
Introduction: History and Where We Are Headed

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Abstract While medical devices have been derived and used since at least ancient Egypt, means of verifying their biologic safety to patients (biocompatibility) and regulations requiring and governing such pre-use evaluation (testing) are much more recent. Less than a century has seen the modern approach, with testing dictated by type, and duration, of patient contact are much more recent. Such requirements first arise in the 1960s due to concerns with materials migrated from a device into the patient body. The science and complexity of testing involved are continuously evolving (accelerated by concerns as to the safety of silicones in the late 1980's) and have also served to drive the growth of the medical device market (now nearly a third the size of the pharmaceutical market) and the innovations and complexity of devices and device/drug combinations.

Keywords Adverse effects on patients · Biocompatibility · Biodegradation of material or device · Breast implants · Center for Devices and Radiological Health · Constituent materials in the device · Cooper Committee · Cumulative duration of contact · Dalkon Shield · Dr. John Autian · Food, Drug, and Cosmetic Act · IDE · Leachables · Medical Device Amendments · Medical device industry · Patient contact mode and duration · Patient exposure parameters · Safe Medical Devices Act · Tripartite

The medical device industry in the Unites States and worldwide is immense in its economic impact, scope (between 92,000 and 145,000 different devices are produced in the United States by ~12,000 different manufacturers employing some 370,000 people; it is believed that ~2100 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 2013; MDDI 2013; Nugent 1994). 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

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these kinds of products, not as quantitative or modern as those employed for foods, drugs, and pesticides, and continue to be in a state of flux. Regulation of the preclinical safety evaluation of such devices is, in fact, fairly recent. It is only with the Medical Device Amendments (to the Food, Drug, and Cosmetic Act) of 1992 that devices have come to be explicitly regulated at all and with the Safe Medical Devices Act of 1993, the Medical Device Amendments of 1992, and subsequent laws that regulation of devices for biocompatibility became rigorous. The FDA's publication of their "Use of ISO-10993" document in June of 2016 marks the most recent regulatory guidance (FDA 2016).

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, latex present in gloves, and a wide range of other devices) have largely faded from public and professional memory by the beginning of the twenty-first century, to be replaced by phthalates, BPA (bisphenol amine), and heavy metals.

1.1 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 over the period of patient contact. Some manufacturers believe that biocompatibility is sufficiently indicated if their devices are made of "medical grade material," ASTM standard metals, or materials approved by FDA as direct or indirect food additives. The term "medical grade" does not have an accepted legal or regulatory definition and can be misleading and assigned 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 in the file. More to the point, as the extent of required data and testing is expanded by regulatory antibiotics, what constitutes adequate testing is a moving target as time passes.

There is no universally accepted definition for biomaterial or 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 device manufacturer (and not those providing the constituent materials or parts) is responsible for understanding biocompatibility tests and selecting currently accepted methods which best demonstrate:

- The lack of adverse biological response from the constituent materials in the device
- The absence of adverse effects on patients

Diversity of the materials used, types of medical devices, nature and duration of patient exposure, 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 complicate safety considerations, as does the increased scope of combination device/drug products (CFR 1992).

Biocompatibility describes the state of a biomaterial within a physiological environment without the material adversely affecting the tissue or (if there is systemic exposure, the body) the body adversely affecting the material. Biocompatibility is the end product of chemical and physical interactions between the material and the tissue/body and the biological response to these reactions. Unlike with drugs or biologics, adverse effects can be due not only to chemical effects but to physical effects associated with surface characteristics of a device (Gad and Gad-McDonald 2015).

Biocompatibility tests are used to predict and therefore avoid significant adverse reactions and establish the absence of any harmful effects of the component material. Such tests help to determine the potential risk which the material may pose to the patient. The proper use of biocompatibility tests can lead to the rejection of potentially harmful materials from use in devices 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 "polycarbonate 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 and duration 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 use. Conditions of manufacturing, packaging, and cleaning can also be critical.

The need for biocompatibility testing and the extent of such testing that should be performed depend on numerous factors which are presented and considered in Chap. 2. These factors include the type of device, intended use, liability, degree and duration of patient contact, nature of the components, nature of potentially expressed patient population (does it include pediatric patients), and potential of the device to cause harm (Gad and Gad-McDonald 2015). 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 (including sterilization mode and packaging) or material as closely as possible and should demonstrate the biocompatibility of a material or device for a specific intended use or range of uses. 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 if they have direct or indirect patient contact (DiSilvo 2009). 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.

1.1.1 Fundamentals of Biocompatibility Tests

Biocompatibility is generally demonstrated by tests utilizing fundamental 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 relevant to biocompatibility testing of devices constructed from multiple materials. In addition, medical devices are an unusual test subject in toxicity testing. As will be discussed, 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 or contaminants introduced during manufacture, 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 for assessment. 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 (Boutrand 2012). Additionally, it is important to make use of exaggerated conditions, such as using higher levels of exposure, exaggerated temperature of extraction, and longer contact durations or multiple other factors more severe than the actual use conditions. Identifying and subsequently ensuring an acceptable exposure level that is multiple factors below the lowest toxic level is the general, and expected, practice.

Historically, 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, and indeed longer-term and more rigorous tests are now being required. A complication for biocompatibility testing compared with pharmaceuticals is that all testing must be performed before there is any clinical evaluation or use.

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 a blood-contacting device would be different from those applicable to a urethral catheter. Also, the degree and nature of required biocompatibility assurance depend 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 as introduced into the body does not adversely affect the body during the long period of use (Greco 1994). The possibility of biodegradation of material or device cannot 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 (USP 2006). 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. The foreign body response mounted by the body has acute, midterm, and long-term components which are generally predictable. 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 have possible limited toxicity. Toxicity can arise from leachable components of the material previously used without adverse effect 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 result 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 a biocompatibility assessment 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 evaluated 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 its 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 a suitable alternate material.

1.2 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 2013), 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, historically devices could be considered as belonging to one of nine categories (North American Industrial Classification System): surgical and medical instruments, ophthalmic, dental, lab apparatus, irradiation, specialty devices, medical/surgical supplies, in vitro diagnostics, and electromedical.

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

1.3 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 US 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 H (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.

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 rigor-

ous. The actual current guidelines for testing started with the USP guidance on biocompatibility of plastics. A defined regulatory approach sprang 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 announced acceptance of International Standards Organization (ISO) 10,993 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 for drugs in this area.

Independent of FDA initiatives, the USP and ASTM have promulgated test methods and standards for various aspects of establishing the safety of drugs (such as the 2013 standards for measurement of heavy metals in extractable materials from devices), 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 served 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 led 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). The third was associated with toxic shock syndrome (TSS) caused by super absorbant tampons.

1.4 Nonspecific Regulatory Considerations

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

1.4.1 Good Laboratory Practices

The original promulgation of GLPs was by the US 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 US 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 Community 1991). The FDA last revised the GLP regulations in 1989 (FDA 1986).

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), be 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).

1.4.2 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.

1.4.3 Regulations Versus Law

A note of caution must be inserted here. The law (the statute promulgated 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 with regulation. For example, the regulations on the PMA process is described in 21 CFR 312 (FDA 2013), 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 FDLI (2013).

Laws authorize the activities and responsibilities of the various federal agencies. All proposed laws before the US Congress are referred to committees for review and approval. The committees responsible for FDA oversight are summarized on Table 1.1. 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.

1.4.4 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 covering almost a third of the economy of the United States. Medical devices are overseen by the CDRH, headed by a director.

Table 1.1 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

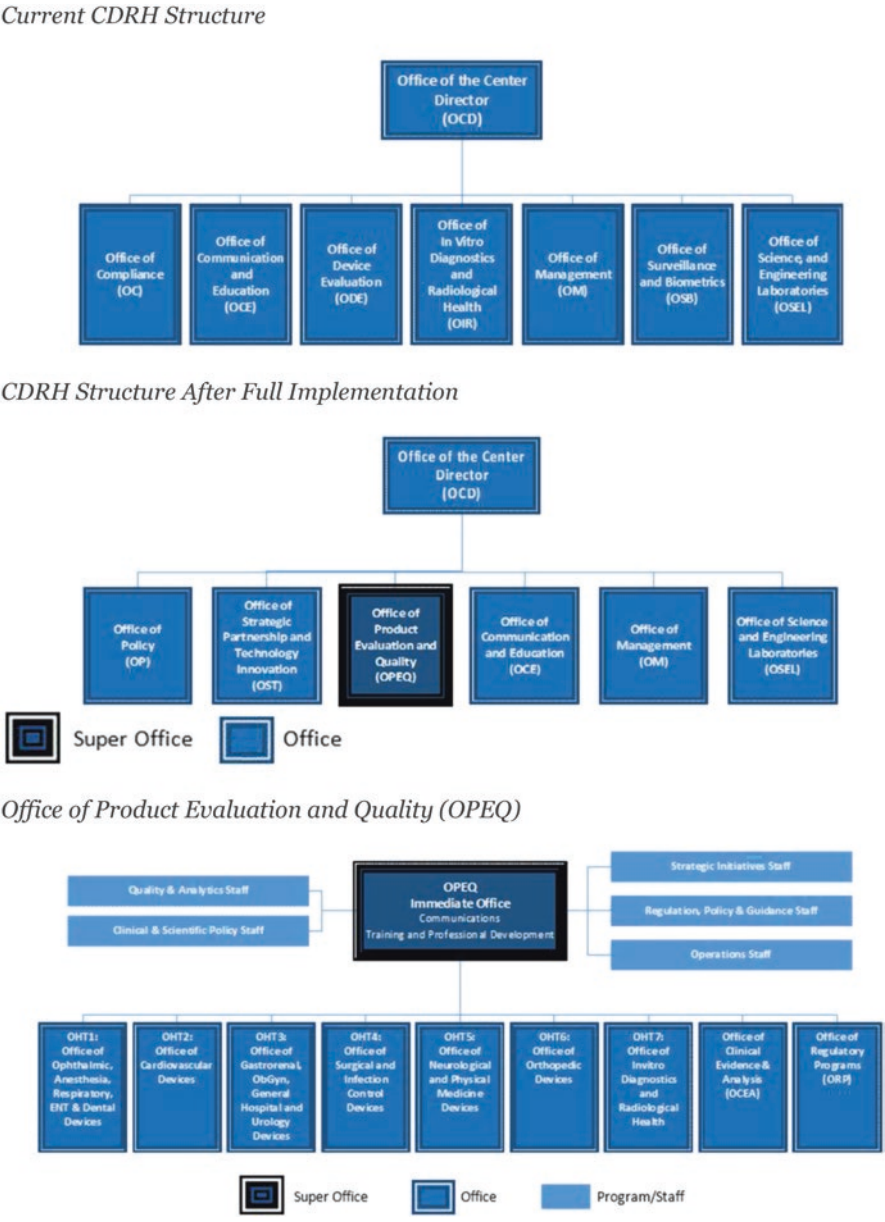

Fig. 1.1 Center for Devices and Radiologic Health (CDRH) Organizational Structure

Drugs are overseen primarily by the Center for Drug Evaluation and Research (CDER) (though some therapeutic or healthcare entities are considered as biologically derived and therefore regulated by the Center for Biologics 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 guidance for 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 Chap. 2.

Modern regulation of the biological safety of medical devices and the materials that they are composed of begins in the late 1950s with concern over the potential risks arising from chemical moieties in plastics migrating into drugs. Prior to this time, most drugs and infusion solutions had been stored and dispensed or delivered from glass containers. This was advanced by the works of Dr. John Autian, who founded the Drug-Plastic Research Laboratory at the College of Pharmacy at the University of Texas. His initial publication on the toxicology of phthalate esters (Calley et al. 1966) lead to the testing and plastics designations section (for medical "closures") in the *United States Pharmacopeia*. The resulting testing requirements are shown in Table 1.2.

These testing guidelines, being all that was available, were used to evaluate the biological safety of medical devices and nonmetal biomaterials.

The next step was the development of the tripartite, originally developed jointly by Canada, the United Kingdom, and the United States (a group subsequently joined

Table 1.2 Innovative areas of medical device (The Wilkerson Group 2013)

Rank	Product	Revenue growth rate (%) (years)	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 & Sullivan

by France) in 1986 (FDA 1986). These guidelines first presented a classification of devices by type and duration of patient exposure.

With a few years of exposure, this guidance evolved into the ISO 10993 system.

1.5 Potential Patient Exposure Parameters (Routes, Regimens, Quantities, and Durations) as a Principal Determinant of Risk

Unlike drugs, food additives, pesticides, biologics, industrial chemicals, or consumer products, the biologic safety (biocompatibility) of medical devices is not determined relative to known administered doses of substances nor for the most part (see the chapter on leachables and extractables [L&Es] and determination of qualified safety levels – which for devices are called tolerable exposures or TEs – for the exception to this) are the precise chemical entities to which patients (or cellular or animal models) are exposed/identified (Gad and Schuh 2018; Gad and Gad-McDonald 2015).

Rather, we use defined biological test systems to evaluate effects in terms of responses to define contact between the device and potential patients. That is, we use bioassays.

The potential interactions between a medical device and patients are determined by three factors (which are incorporated into the ISO 10992-1 testing matrix).

1.5.1 What Is the Type or Route of Patient Exposure?

Which patient tissues have contact with a device is overwhelming the determinant what happens at this direct tissue/device surface interface that presents potential adversity. While there are exceptions (genotoxicity, pyrogenicity and for the most part sensitization), physical and chemical interactions by which the host and device modify each other occur at this interface or very near it.

Devices may have more than one type of tissue contact, which complicates evaluation of potential interactions.

1.5.2 How Much of the Device Contacts Patient Tissues?

The measurement here is not (generally) of the mass of the device, but rather of the surface area.

When the test in question consists of direct device to tissue contact (such as with implantation), the device itself determines the quantity of surface to tissue contact (such as in implantation studies). That said, in many cases, what is tested is an

Table 1.3 Volume/surface area

Form of material	Thickness	Amount of *sample* for each 20 mL of extracting medium[a]	Subdivided into
Film or sheet	<0.5 mm	Equivalent of 120 cm^2 total surface area (both sides combined)	Strips of about 5 × 0.3 cm
	0.5–1 mm	Equivalent of 60 cm^2 total surface area (both sides combined)	
Tubing	<0.5 mm (wall)	Length (in cm) = 60 cm^2/(sum of ID and OD circumferences)	Sections of about 5 × 0.3 cm
	0.5–1 mm (wall)	Length (in cm) = 60 cm^2/(sum of ID and OD circumferences)	
Slabs, tubing, and molded items	>1 mm	Equivalent of 60 cm^2 total surface area (all exposed surfaces combined)	Pieces up to about 5 × 0.3 cm
Elastomers	>1 mm	Equivalent of 25 cm^2 total surface area (all exposed surfaces combined)	Do not subdivide[b]

[a]When surface area cannot be determined due to the configuration of the specimen, use 0.1 g of elastomer or 0.2 g of plastic or other polymers for every 1 mL of extracting fluid
[b]Molded elastomeric closures are tested intact

extract solution derived from the actual device. In these situations, testing practices and guidelines call for determining the potential surface area having contact with patient tissues and then using a guideline (ISO 10993)-prescribed volume of one or more vehicles (solvents, really) to be used in performing extractions so as to provide a liquid which can be used in subsequent actual tests (Table 1.3).

In some cases, the shape of a device component having patient contact is so irregular that it is not possible to accurately calculate a surface area, so rather the weight of the device determines the volume of extraction solution (Table 1.4).

In most cases, two separate extraction fluids are used – a polar (such as water, saline, or ethanol in water) and a nonpolar (such as hexane). See Table 1.1 for a list of extraction fluids. These are intended to simulate the principal physicochemical components of the body – water (~67% of body volume on average) and lipids. The original USP list of solvents was more extensive, as it was intended to reflect the range of solvents which were used in the formulation of medicants in contrast with the plastic and elastomer containers ("closures") for drugs. This broader range of solvents is still reflected in the (mouse) acute systemic toxicity test.

An exception is in the case of mammalian in vitro genotoxicity tests, where extraction is directly into culture medium with serum. Here, the underlying thought is that the medium stands in place of blood, which would serve to transfer any potential genotoxic moiety from the surface of the device to a potential susceptible target tissue.

Table 1.4 Extraction fluids

Common name: Cottonseed oil (CSO)
Chemical name: NA
Molecular weight: NA
Formula: Mixture of natural products; glycerides of palmitic, olive, and linoleic acids
Density: 0.915–0.921 g/ml
Volatility: Low
Solubility/miscibility: Soluble in ether, benzene, chloroform, and DMSO. Slightly soluble in ethanol
Biological considerations: Orally, serves as energy source (and therefore can alter food consumption and/or body weight). Prolonged oral administration has been associated with enhanced carcinogenesis
Chemical compatibility/stability considerations: Thickens upon prolonged exposure to air. Available in USP grade.
Uses (routes): In extractions and as a vehicle for oral, dermal, vaginal, rectal and subcutaneous administration
Common name: DMSO/dimethyl sulfoxide
Chemical name: Sulfinylbis[methane]; CAS #67–68-5
Molecular weight: 78.13
Formula: C_2H_6OS
Density: 1.100 g/ml at 20 °C
Volatility: Medium
Solubility/miscibility: Soluble in water, ethanol, acetone, ether, oils
Biological considerations: Oral LD50 (rats) = 17.9 ml/kg. Repeated dermal exposure can defat skin. Repeated oral exposure can produce corneal opacities. Not cytotoxic to cells in primary culture at less than 0.05% (V/V). Intraperitoneal LD50 (mice) = 11.6 ml/kg
Chemical compatibility/stability considerations: Very hydroscopic liquid. Combustible
Uses (routes): All, as a carrier at up to 5% to enhance absorption
Common name: Ethanol; EtOH
Chemical name: Ethyl alcohol; CAS #64–17-5
Molecular weight: 46.07
Formula: C_2H_5OH
Density: 0.789 g/ml
Volatility: High, but declines when part of mixture with water
Solubility/miscibility: Miscible with water, acetone, and most other vehicles
Biological considerations: Orally, will produce transient neurobehavioral intoxication. Oral LD50 (rats) = 13.0 ml/kg. Intravenous LD50 (mice) = 5.1 ml/kg
Chemical compatibility/stability considerations: Flammable colorless liquid available USP grade
Uses (routes): Extraction solvent vehicle for dermal and oral, though can be used in lower concentrations for most other routes. Volume of oral instillation should be limited to 5 ml/kg
Common name: Polyethylene glycol (PEG)
Chemical name: NA
Molecular weight: 400 (approximate average, range 380–420)
Formula: $H(OCH_2CH_2)_nOH$

(continued)

Table 1.4 (continued)

Density: 1.128 g/ml
Volatility: Very low
Solubility/miscibility: Highly soluble in water. Soluble in alcohol and many organic solvents
Biological considerations: Employed as water-soluble emulsifying/dispersing agents. Oral LD50 (mice) = 23.7 ml/kg. Oral LD50 (rats) = 30 ml/kg
Chemical compatibility/stability considerations: Do not hydrolyze or deteriorate on storage and will not support mold growth. Clear, viscous liquid
Uses (routes): As extraction solvent for oral administration as a vehicle full strength or mixed with water. Total dosage of PEG-400 should not exceed 5–10 ml
Common name: Saline
Chemical name: Physiological saline; isotonic salt solution
Molecular weight: 18.02
Formula: 0l9% NaCl in water (weight to volume)
Density: As water
Volatility: Low
Solubility/miscibility: As water
Biological considerations: No limitations – preferable to water in parenteral applications
Chemical compatibility/stability considerations: None
Uses (routes): Extraction solvent all except periocular

Source: Gad and Chengelis (1992); Lewis (2012)

1.5.3 What Is the Cumulative Duration of Contact of a Device with a Patient?

The cumulative duration of contact is critical in determining both the potential risk to patients and the extent of testing required. Very short-term exposures generally require just the basic three tests (cytotoxicity, irritation in the appropriate tissue, and sensitization). With longer duration of exposure, the range and scope of potential interactions between host and devices increase, calling for a more extensive range of tests.

The “continental divide” is 30 days, after which exposure is considered “permanent.” The basis for this is by this time, the body’s adaptive immune system has had time to fully respond to the surface of the device and any moieties which may be released from the device into the body.

Notice that duration is defined as cumulative if the identical type of device is sequentially replaced with new units on a regular basis (such as occurs with catheters or wound dressings) then it is as if a single device was left in place for the entire time the device type had patient contact.

Note also that by definition, implanted devices have “permanent” durations of contact. It is important to differentiate that components/tools (such as guidewires or tracers) which are used to put an implant in place do not have permanent contact (rather their contact is less than 24 hours); the implanted devices themselves are permanent.

The first special case is that of resorbable devices. These are almost always permanent, as it takes more than 30 days for the device to be (effectively) dissolved into the body and have much greater potential to generate/release chemical components that are distributed throughout the body.

The second special case is that of respiratory devices – devices meant to support patient breathing and in some cases to administer/infuse drug materials by the pulmonary route. The direct patient contact with these devices is limited to external skin where the devices generally touch the face, and the epithelial tissue on the inside of the nose and/or mouth; however, hair flow through the devices into breathing channels has the opportunity to pick up and carry on materials from the interior surface of the device as it passes through, progressing perhaps all the way into a patients deep dungs. A further complication is that the devices have significant use in the very young (neonates, pediatrics, and juveniles) and very old and in individuals who are already significantly compromised in their breathing.

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