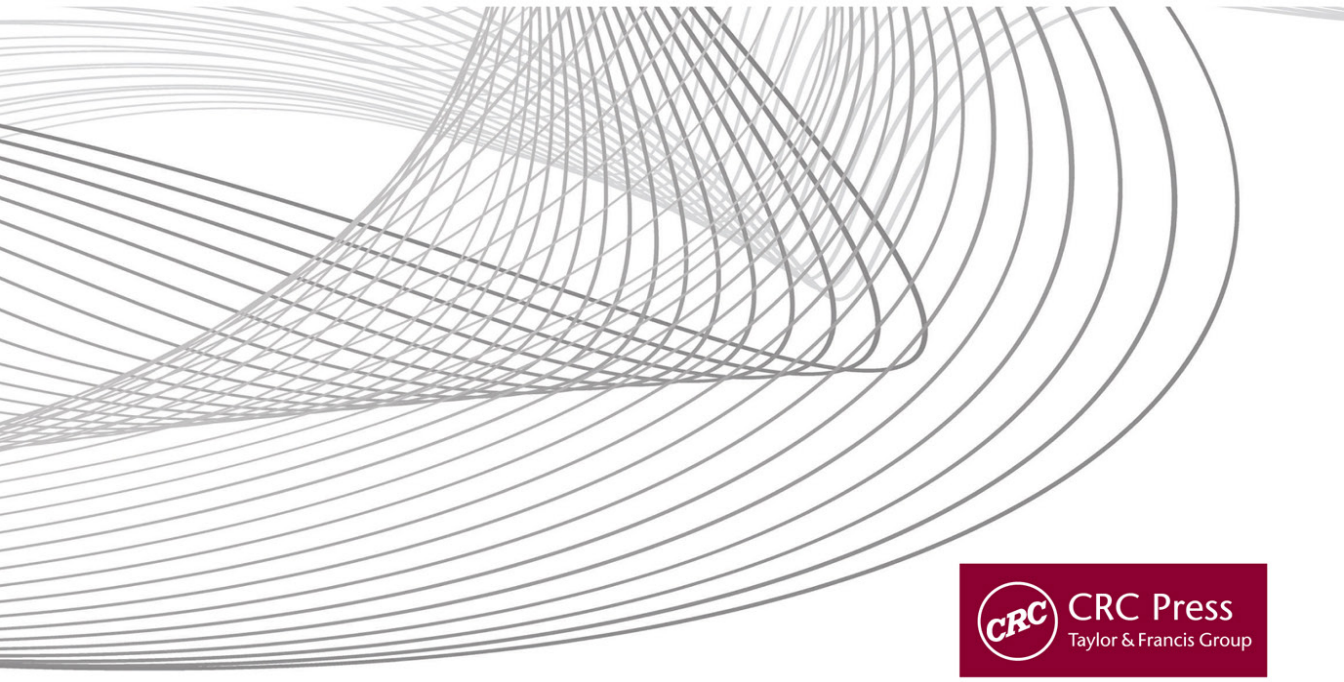
MEDICAL DEVICES

A PRACTICAL GUIDE

Edited by

Prakash Srinivasan Timiri Shanmugam



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Medical Devices

This book provides an overview of the wide variety of medical devices that are an integral part of clinical practice. This practical book includes descriptions of medical devices by both clinical specialty and purpose, thus ensuring that a wide variety of devices are included, covering important elements such as body contact, duration of contact, the mechanism of each device, its intended use, single and/or multiple use, benefits and any side/adverse/toxicological effects to the patient, and how to avoid user error. Authored by clinicians, researchers, and educators who are experienced in medical device use, regulation, and research, the content will be of benefit to postgraduate clinicians and employees of medical device companies.

Medical Devices

A Practical Guide

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Prakash Srinivasan Timiri Shanmugam

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Introduction 1

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Medical devices play an important role in the delivery of many health care services. "Medical device" means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations
- and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means (1)

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception
- products specifically intended for the cleaning, disinfection or sterilization of devices

The term applies to everything from common medical supplies such as latex gloves and syringes to advanced imaging equipment and implantable devices such as cardiac defibrillators. The medical device industry is thus an important component of the larger health care system and plays an essential role by developing new medical technologies that can improve the ability to diagnose and treat illness. Some types of medical devices include:

- single-use devices (i.e. syringes, catheters)
- implantable (i.e. hip prothesis, pacemakers)
- imaging (i.e. ultrasound and CT scanners)
- medical equipment (i.e. anesthesia machines, patient monitors, hemodialysis machines)
- software (i.e. computer aided diagnostics)
- in vitro diagnostics (i.e. glucometer, HIV tests)

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- personal protective equipment (i.e. mask, gowns, gloves)
- surgical and laboratory instruments

BACKGROUND

As early as 2000 to 5000 years ago, many ancient civilizations used tools such as forceps, knives, scalpels, saws, lancets, needles, trocars, cauteries and knives for several medical procedures. Scalpels were used to make big incisions across the abdomen, and clean, precise incisions on the arms, neck and legs. Punctures in various parts of the body were made using needles. Hooks held up blood vessels and skin, and lifted and moved tissue during a medical procedure. Hand drills were used to remove parts of the skull to access the brain, to either cut out portions in a lobotomy or to remove dead tissue from the body. Forceps, an extremely versatile tool during surgery, were used to grasp or position tissues, immobilize blood flow and hold skin together while adding or removing stitches. Suturing techniques used crude forms of needle and thread. Early procedures included tracheotomy, amputations, bloodletting, cataract surgery, bone surgeries, removal of bladder stones, trepanation (making a hole in the skull), organ removal, etc. The earliest instruments used in these procedures were made of stone, flint or obsidian, and later on from metals like silver, gold and bronze.

From about the 1st century CE to the 17th century, most medical procedures involved the treatment of injuries of soldiers at war on the battlefields, or the ailments of the very rich. Devices were used to treat battleground wounds received from arrows, knives, sabers, guns and cannons. With the formalization of the scientific method in the 17th century such devices became more prevalent. Many medical devices were manufactured by doctors or small companies and sold directly to the public with no government standards or oversight for safety or effectiveness. Hospitals were created as a place where soldiers and patients could be treated by doctors with access to specialized equipment and care. Universities began teaching science, medicine, anatomy and medical-related topics. Medical knowledge and know-how continued to expand and evolve. Advances were made in the areas like ophthalmology, optometry, prostheses, catheterization with devices like syringes for the removal of cataracts, eyeglasses, metallic or wooden artificial limbs and metallic catheters respectively.

Discovery of what would be considered a medical device by modern standards dates as far back as c. 7000 BC in Baluchistan where Neolithic dentists used flint-tipped drills and bowstrings. The study of archeology and Roman medical literature also indicates that many types of medical devices were in widespread use during the time of ancient Rome. In the United States it wasn't until the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1938 that medical devices were regulated. Later, in 1976, the Medical Device Amendments to the FD&C Act established medical device regulation and oversight as we know it today (2).

The road to modern medicine has been a long one, and doctors have come up with a variety of tools along the way. But some of the early iterations were, shall we say, a little crude. Here are some of the more cringe-inducing instruments from medicine's past.

Artificial leeches: When in the 1800s live leeches were unavailable, or perhaps too gross, this metal cylinder with blades performed the same function. Its rotating blades cut into the skin, while the tube suctioned the blood out. A similar tool, called a scarificator, used up to ten spring-loaded blades. They quickly sliced into the skin and then the device was heated to create a vacuum.

Hernia tool: Recognizing that the human body could often patch things up better than they could, doctors in the 1850s had a tool specifically for hernias. Once doctors repaired the tear in the muscle or tissue, they would insert the hernia tool into the area. This thing would be in place for about a week while scar tissue formed on it to help seal your repaired hernia.

Amputation saw: Medicine also has a long history of doctors lopping off problems they didn't yet know how to fix, such as infections. From the pre-antibiotic bacteria of old to the antibiotic-resistant bacteria of today, infection has always been a major reason for amputations. But doctors often took pride

in the instruments used for this grisly purpose. Saws like this had decorative swirls, grooves and other designs that were, ironically, probably also a place for germs to breed.

Ecraseur: Used in the 19th century, this instrument strangled uterine and ovarian tumors as well as hemorrhoids. Its wire loop or chain was placed around the base of the unwanted growth and gradually tightened. That would eventually either cut through the base of the growth or cut off its blood supply until it gave up and dropped off. Doing this was painful, particularly with hemorrhoids, but experts of the day argued that the pain was short-lived compared with cutting.

Arrow remover: When a patient in the 1500s sported a protruding arrow, the medical professionals didn't just yank it out. Instead, they held the shaft of the arrow in the center barrel of a scissor-like arrow remover. But unlike scissors, the sharp edges of the blades faced away from the center. So, as if having an arrow stuck in you wasn't bad enough, the blades cut the skin so that the arrow's head could be removed without much further injury.

Speculum: Long before the speculum was actually called that, there were tools for getting an intimate look at a woman's reproductive organs. In the 1600s, it was a rather frilly-looking sort of inverted salad tongs. Once the leading end was inserted into the entry of the vagina or other orifice, the user would turn the crank at the other end to widen the opening for a better view.

Syringe: Syringes are still in use today, but this simple piston syringe was special. With its long, thin tube and pump, it was way bigger than the hypodermics we use today. It was used in the 1500s to inject mercury as a treatment for syphilis, often contracted by amorous sailors on the high seas. With such a huge syringe, the good news is that you didn't get stabbed with it. The bad news is that it was a urethral syringe, so the injection went directly into the penis through its natural opening. Worse yet, mercury often killed people long before syphilis complications (3).

The 1800s was a groundbreaking era for medical devices, therapeutic and medical inventions and the development of modern medicine. In 1867, Joseph Lister published his "Antiseptic Principle of the Practice of Surgery". This was one of the most seminal and pivotal moments in medical science that would ultimately lead to cleaner operating theatres, more successful outcomes and higher survival rates of patients. Louis Pasteur and Robert Koch identified "germs" as the cause of many diseases around the world (4). In the 19th century, devices such as the stethoscope, the hypodermic syringe, the ophthalmoscope, the electrocardiogram, hearing aids, the kymograph and nitrous oxide as an anesthetic were brought to market. In addition, drugs such as quinine, aspirin and cholera vaccines were also discovered, significantly changing the health outcomes of the public. The design of devices such as forceps, knives, scalpels, saws, lancets, needles, trocars, cauteries and knives continued to evolve with the use of materials like steel. The 20th century saw an explosion of medical devices and procedures that included the cardio defibrillator, hip and knee replacements, heart surgeries, laparoscopes, dialysis machines, infusion pumps, insulin pumps, balloon catheters, disposable catheters, disposables, the iron lung, heart lung machines, inhalers, prostheses, cardiovascular devices, respirators, ventilators and implants such as stents and pacemakers. The growth of medical devices has been exponential in the last 100 years.

TERMS AND DEFINITIONS

"**Accessory to a medical device**" means an article which, while not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s).

"**Active medical device**" means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices.

"**Active therapeutic device**" means any active device used, whether alone or in combination with other devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or disability.

"**Active device intended for diagnosis and monitoring**" means any active device used, whether alone or in combination with other devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.

"**Adverse event**" means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

"**Biomaterial**" is a material brought into contact with living tissue for the treatment of medical and dental conditions.

"**Calibrator**" means a measurement reference material used in the calibration of a device.

"**Companion diagnostic**" means a device which is essential for the safe and effective use of a corresponding medicinal product to identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

"**Common specifications**" **(CS)** means a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.

"**Clinical performance**" means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

"**Compatibility**" is the ability of a device, including software, when used together with one or more other devices in accordance with its intended purpose, to perform without losing or compromising the ability to perform as intended, and/or integrate and/or operate without the need for modification or adaption of any part of the combined devices, and/or be used together without conflict/interference or adverse reaction.

"**Conformity assessment**" means the process of demonstrating whether the requirements of a regulation relating to a device have been fulfilled.

"**Corrective action**" means action taken to eliminate the cause of a potential or actual non-conformity or other undesirable situation.

"**Custom-made device**" means any device specifically made in accordance with a written prescription of any person authorized by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs. However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorized person shall not be considered to be custom-made devices.

"**Device deficiency**" means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

"**Falsified device**" means any device with a false presentation of its identity and/or its source and/or its Conformitè Europëenne (CE) marking certificates or documents relating to CE marking procedures. This definition does not include unintentional non-compliance and is without prejudice to infringements of intellectual property rights.

"**Harmonized standard**" means a European standard as defined in point (1)(c) of Article 2 of Regulation (EU) No 1025/2012.

"**Implantable device**" means any device, including those that are partially or wholly absorbed, which is intended to be totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by clinical intervention, and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device.

"**In vitro diagnostic medical device**" means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- concerning a physiological or pathological process or state
- concerning congenital physical or mental impairments
- concerning the predisposition to a medical condition or a disease
- to determine the safety and compatibility with potential recipients
- to predict treatment response or reactions
- to define or monitor therapeutic measures
- specimen receptacles shall also be deemed to be in vitro diagnostic medical devices

"**Invasive device**" means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.

"**Investigational device**" means a device that is assessed in a clinical investigation.

"**Legacy devices**" are considered to include all devices previously CE marked under the European Medical Devices Directive 93/42/EEC (MDD) or Active Implantable Medical Devices Directive 90/385/EEC (AIMDD).

"**Life cycle**" means a series of all phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

"**Nanomaterial**" means a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm; fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials.

"**Non-viable**" means having no potential for metabolism or multiplication.

"**Notified body**" means a conformity assessment body designated in accordance with this Regulation.

"**Performance evaluation**" means an assessment and analysis of data to establish or verify the scientific validity and the analytical and, where applicable, the clinical performance of a device.

"**Recall**" means any measure aimed at achieving the return of a device that has already been made available to the end user.

"**Risk**" means the combination of the probability of occurrence of harm and the severity of that harm.

"**Risk management**" means the systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk.

"**Serious adverse event**" means any adverse event that leads to any of the following:

- a patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring
- death
- serious deterioration in the health of the individual being tested or the recipient of tested donations or materials that results in any of the following:
  - life-threatening illness or injury
  - permanent impairment of a body structure or a body function
  - hospitalization or prolongation of patient hospitalization
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
  - chronic disease
  - fetal distress, fetal death or a congenital physical or mental impairment or birth defect

"**Single-use device**" means a device that is intended to be used on one individual during a single procedure.

"**System**" means a combination of products, either packaged together or not, which are intended to be inter-connected or combined to achieve a specific medical purpose.

"**Unique device identifier**" ("**UDI**") means a series of numeric or alphanumeric characters that are created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market.

"**Withdrawal**" means any measure aimed at preventing a device in the supply chain from being further made available on the market.

CLASSIFICATION OF MEDICAL DEVICES

The Food and Drug Administration (FDA) has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

Class 1 – Low Risk

There are currently approximately 780 Class I devices on the market. General controls include Adulteration/Misbranding, Electronic Establishment, Registration, Electronic Device Listing, Premarket Notification, Quality Systems, Labeling and Medical Device Reporting (MDR).

Examples: Corrective glasses and frames, manual wheelchairs.

Type of certification: Self-certification/self-declaration.

Class 1s – Low Risk (Sterile)

Examples: Personal protection kits, sterile urine bags, etc.

Type of certification: Notified body.

Class 1m – Low Risk (Measuring Body Attributes)

Examples: Stethoscopes, weighing balance.

Type of certification: Notified body.

Class 1r – Low Risk (Reused Device)

Examples: Surgical forceps (all types of SS/Tit surgical equipment sterilized and reused by hospitals).

Type of certification: Notified body.

Class IIa – Medium Risk

Examples: Orthodontic wires, surgical gloves, lancets.

Type of certification: Notified body.

Class IIb – Medium to High Risk

Most devices are classified as Class II, an intermediate-risk device that is subject to "special controls" to assure safety. The majority of Class II devices are subject to premarket review and clearance by FDA through the 510 (k)-premarket notification process and may have rigorous review requirements in line with a Class III device. There are currently over 800 Class II devices on the market.

Examples: Orthopedic nails and plates, intra-ocular lenses, pregnancy test kits, incubators for babies.

Type of certification: Notified body.

Class III – High Risk

These devices are subject to the most rigorous review process that includes general controls, special controls and premarket approval. There are fewer than 120 Class III devices currently on the market.

Examples: Pacemakers, prosthetic heart valves, cardiovascular sutures, brain spatulas, drug-device combination products.

Type of certification: Notified body.

Medical Device Classification: 21 CFR 862–892

Most medical devices can be classified by finding the matching description of the device in Title 21 of the Code of Federal Regulations (CFR), Parts 862–892. FDA has classified and described over 1,700 distinct types of devices and organized them in the CFR into 16 medical specialty panels such as cardiovascular devices or in vitro diagnostics.

862 = Chemistry/Toxicology
864 = Hematology/Pathology
866 = Immunology/Microbiology
868 = Anesthesiology
870 = Cardiovascular
872 = Dental
874 = Ear, Nose and Throat
876 = Gastro/Urology
878 = General Plastic Surgery
880 = General Hospital
882 = Neurological
884 = Obstetrical/Gynecological
886 = Ophthalmic
888 = Orthopedic
890 = Physical Medicine
892 = Radiology Regulations

For each of the devices classified by the FDA, the CFR gives a general description including the intended use, the class to which the device belongs (i.e. Class I, II or III) and information about marketing requirements. Your device should meet the definition in a classification regulation contained in 21 CFR 862–892.

MATERIALS USED IN MEDICAL DEVICES

The most common classes of materials used in the devices are metals, polymers, ceramics and composite (Table 1.1). These four classes are used singly and in combination to form most of the implantation devices available today. Metals are particularly inert, ceramics may be inert, active or resorbable and polymers may be inert or resorbable in nature. Biomaterials must be nontoxic, noncarcinogenic, chemically inert, stable and mechanically strong enough to withstand the repeated forces of a lifetime (5).

In the development of medical devices, selecting appropriate material for each part is a vital step, one which demands an understanding of issues ranging from physical performance and manufacturing constraints to fund limitations and supply chain logistics. There are few "trivial" components in a medical device, and identifying materials for all but the most direct demands a robust decision process to check that appropriate options are assessed. In device design, several essential factors need to be considered when deciding whether a material, and its specific grade, are appropriate for use on a component. Biomaterial used in the devices and implants should have some important properties in order for long-term usage in the body without rejection.

Materials testing: Materials are tested to determine the properties of biomaterials used in various devices. The data thus obtained can be used in specifying the suitability of materials for various applications like medical devices and implants. The materials chosen must be able to support the device's function. Safety is the most important reason material testing is done, and it also prevents the failure of devices. Standard test methods have been established by such national and international bodies as the International Organization for Standardization (ISO), with headquarters in Geneva, and the American Society for Testing and Materials (ASTM), Philadelphia.

Biocompatibility

Biocompatibility is a key demand for several medical devices, especially newer drug delivery devices which must be made of materials suitable for contact with both the drug and the user. Materials that are biocompatible are called biomaterials, and biocompatibility is a descriptive term which indicates the ability of a material to perform with an appropriate or specific host response, in a device application. For new materials not already approved, extensive material test programs could be required to check extractables and leachables, toxicity or irritation, depending on the application and risk. For considerations such as long-term implantation or primary drug packaging, where permeability to substances including moisture or oxygen can also be a vital property, these issues can be the dominant factor driving material/material grade selection. It should not adversely affect the local and systemic host environment of interaction (bone, soft tissues, ionic composition of plasma, as well as intra- and extracellular fluids). Biocompatibility refers

TABLE 1.1 Classification of Materials Used in Medical Devices

MATERIALS CLASSIFICATION	
MATERIALS	*SUBCATEGORIES*
Metals	Gold, tantalum, Ti6A14V, stainless steel, Co-Cr alloys, titanium, nitinol
Polymers	Ultra-high molecular weight polyethylene (UHMWPE), polyurethane (PE), polyurethane (PU), polytetrafluoroethylene (PTFE), polyacetal (PA), polymethylmethacrylate (PMMA), polyethylene terephthalate (PET), silicone rubber (SR), polyetheretherketone (PEEK), poly (lactic acid) (PLA), polysulfone (PS)
Ceramics	Alumina, zirconia, carbon, titania, bioglass, hydroxyapatite (HA)
Composites	Silica/SR, CF/UHMWPE, CF/PTFE, HA/PE, CF/epoxy, CF/PEEK, CF/C, Al2O3/PTFE

to a set of properties that a material must have to be used safely in a biological organism. A biocompatible material must be noncarcinogenic, non-pyrogenic, nontoxic, non-allergenic, blood compatible and noninflammatory. The operational definition of biocompatible is "The patient is alive so the material must be biocompatible".

Bio Functionality

Bio functionality fulfills a specific function in physical and mechanical terms. The material must satisfy its design requirements in service:

- load transmission and stress distribution (e.g. bone replacement)
- articulation to allow movement (e.g. artificial knee joint)
- control of blood and fluid flow (e.g. artificial heart)
- space filling (e.g. cosmetic surgery)
- electrical stimuli (e.g. pacemaker)
- light transmission (e.g. implanted lenses)
- sound transmission (e.g. cochlear implant)

Toxicology

A biomaterial should not be toxic to the human, unless it is specifically engineered for such requirements (for example a "smart bomb" drug delivery system that targets cancer cells and destroys them). Toxicology for biomaterials deals with the substances that migrate or are released out of the biomaterials. It is reasonable to say that a biomaterial should not give off anything from its mass unless it is specifically designed to do so.

BIOLOGICAL EVALUATION OF MEDICAL DEVICES

Biological safety evaluation and hazard testing of medical devices shall be performed in compliance with ISO 10993 "Biological Evaluation of Medical Devices" series as the international standard. Based on the framework and principles of ISO 10993-1 "Evaluation and Testing", the necessary evaluation items can be selected corresponding to the nature and duration of exposure of individual medical devices to the human body. The test method guidelines in the ISO 10993 series generally include lists of multiple test methods for each evaluation item. ISO 10993-3 specifies strategies for risk estimation, selection of hazard identification tests and risk management, with respect to the possibility of the following potentially irreversible biological effects arising as a result of exposure to medical devices:

- acute toxicity
- chronic toxicity
- irritation (eye, skin, mucosal surfaces)
- hypersensitivity
- genotoxicity
- carcinogenicity
- reproductive and developmental toxicity

The international standards have been continuously revised according to the development of science and technology. Accordingly, an appropriate test method must be selected, considering the most current international standards at the time when testing is conducted.

MEDICAL DEVICES REGULATIONS

In the United States, medical devices are regulated by the FDA with an aim of ensuring the safety and effectiveness of the devices. The FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, X-ray systems and ultrasound equipment (6). The basic regulatory requirements that manufacturers of medical devices distributed in the United States must comply with are:

Establishment Registration and Medical Device Listing – 21 CFR Part 807

Owners or operators of establishments that are involved in the production and distribution of medical devices intended for use in the United States are required to register annually with the FDA. This process is known as establishment registration.

Manufacturers must list their devices with the FDA. Establishments required to list their devices include:

manufacturers
contract manufacturers
contract sterilizers
repackagers and relabelers
specification developers
reprocessors of single-use devices
remanufacturers
manufacturers of accessories and components sold directly to the end user
US manufacturers of "export only" devices

Premarket Notification 510(k) – 21 CFR Part 807 Subpart E

A company that wants to market a Class I, II or III device intended for human use in the United States, for which a Premarket Approval (PMA) application is not required, must submit a 510(k) to FDA unless the device is exempt from the 510(k) requirements of the FD&C Act. There is no 510(k) form; however, 21 CFR 807 Subpart E describes the requirements for a 510(k) submission. Before marketing a device, each submitter must receive an order, in the form of a letter, from the FDA which finds the device to be substantially equivalent (SE) and states that the device can be marketed in the United States. This order "clears" the device for commercial distribution (7).

Premarket Approval (PMA) – 21 CFR Part 814

Products requiring PMAs are Class III devices which are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicates through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.

Investigational Device Exemption (IDE) for Clinical Studies – 21CFR Part 812

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect the safety and effectiveness data required to support a PMA application or a Premarket Notification 510(k) submission to FDA. Clinical studies with devices of significant risk must be approved by the FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of nonsignificant risk must be approved by the IRB only before the study can begin.

Quality System (QS) Regulation 21 CFR Part 820

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for the designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

Labeling Requirements – 21 CFR Part 801

The US FDA develops and administers regulations under authority granted by laws passed by Congress that apply to food, drugs, cosmetics, biologics, radiation-emitting electronic products and medical devices. Labeling regulations pertaining to medical devices are found in the following Parts of Title 21 of the CFR.

Medical Device Reporting (MDR) – 21 CFR Part 803

Incidents in which a device may have caused or contributed to a death or serious injury must be reported to the FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for the FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

EU Regulation

EU Regulation of Restriction of Hazardous Substances (RoHS): European Union directives have restricted the use of certain hazardous substances in medical devices and implants. Hazardous substances are categorized per EU Regulation 1272/2008 (Classification, Labelling and Packaging of Substances/Mixtures and Substances Identified in EU Regulation 1907/2006) (REACH: Registration, Evaluation, Authorization, and Restriction of Chemicals). EU 1272/2008 REACH contains a list of all hazardous chemicals. A substance of very high concern (SVHC) contains carcinogenic, mutagenic, reproductive toxic (CMR) substances like N, N-dimethylanilinium tetrakis borate, dibutylin hydrogen borate, perboric acid and restricted substances of endocrine disruptives (EDs), persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB). Chemicals that are substances of very high concern are to be phased out and replaced with safer alternative chemicals (8). In addition to CMR, EDs, PBTs and vPvB, the list extends to flammable gases, flammable aerosols, oxidizing gases, gases under pressure, flammable liquids, flammable solids, self-reactive substances or mixtures, chemicals capable of causing skin corrosion, irritation, serious eye irritation, respiratory/skin sensitization, germ cell mutagenicity or specific target organ toxicity and chemicals hazardous to the aquatic environment or ozone layer. RoHS

specifies maximum levels by weight for the following ten restricted materials. The first six were included in the original RoHS while the last four phthalates were added under RoHS III. The expanded list for RoHS 3 is thus as follows:

- lead (0.1%)
- mercury (0.1%)
- cadmium (0.01%)
- hexavalent chromium (0.1%)
- polybrominated biphenyls (PBB) (0.1%)
- polybrominated diphenyl ethers (PBDE) (0.1%)
- **bis (2-ethylhexyl) phthalate (DEHP) (0.1%)**
- **butyl benzyl phthalate (BBP) (0.1%)**
- **dibutyl phthalate (DBP) (0.1%)**
- **diisobutyl phthalate (DIBP) (0.1%)**

As per RoHS guidelines, device designers are required to replace these chemicals in their products with less hazardous alternatives. The hazardous substances present in any medical device or implant should be less than 0.1 W/W of the device. Acceptable justification must be given if the CMR or endocrine-disrupting substances (for example, lead compounds, other heavy metals, phenols) are present above 0.1% by weight in these device types. The restriction of DEHP, BBP, DBP and DIBP shall apply to medical devices, including in vitro medical devices, and monitoring and control instruments, including industrial monitoring and control instruments, from 22 July 2021. Medical device manufacturers are advised to thoroughly review the conformity assessment procedures applicable to their device to avoid delays in the product review and approval process. In addition to the requirements of RoHS III (EU Directive 2015/863), medical device manufacturers may be subject to other EU directives and regulations addressing the use of hazardous substances and the control of electrical and electronic waste. These include EU Directive 2012/19/EC on Waste Electrical and Electronic Equipment (II), and EU Regulation (1907/2006), as well as EU directives on the disposal of batteries, and on product packaging and packaging waste. According to EU Directive (2011/65/EU) medical devices have to follow the restrictions regarding the use of hazardous substances.

PHASES IN THE LIFE SPAN OF A MEDICAL DEVICE

It is important to recognize that any of these phases can affect the safety and performance of a medical device. Examples of how each phase can create health hazards are described below (9):

Conception and development: The scientific principles upon which a device is based are fundamental to its safety and performance. For example, a cardiac pacemaker should deliver a minute electrical impulse of a certain size and shape that simulates the natural functioning of the heart. Significant deviation from this may compromise safety and performance. The more complex the device, the higher the risk of user error. Soundness of concept and adequacy of design, construction and testing (including verification, validation and clinical trials) require the scrutiny of scientific experts to ensure that design parameters and performance characteristics do not impose unwarranted risks (10).

Manufacture: Functional medical devices are produced when the manufacturing process is adequately managed. However, poor manufacturing management can produce inconsistency in the quality of products, such that non-conforming devices can filter through the production line to the market, even when the original prototype has been well-designed. This consideration has led to the development of good manufacturing practice (GMP) for drugs, biological products and medical devices. Now, GMP is more commonly referred to as "quality systems in manufacturing", and these are addressed later in this guide.

Packaging and labeling: Properly packaged medical devices pose little risk to individuals handling them, even if the medical device is biohazardous. This highlights the importance of well-designed packaging systems in delivering clean, sterile and protected medical devices to the point of use. Shipping is one of the hazards a medical device and its packaging must survive. Subtle damage can result during transportation and handling unless the total packaging system is designed robustly and can withstand various stresses. Well-sealed packaging is essential for those medical devices that must be kept sterile. Labeling is crucial in identifying the medical device and specifying instructions for its proper use. As with drugs, the mislabeling of medical devices can result in serious consequences for the user. Hazard warnings or cautions and clear instructions for use are very important.

Advertising: Advertisement has the potential to create expectations and powerfully influence the belief in a medical device's capabilities. It is important, therefore, that medical device marketing and advertising are regulated to prevent misrepresentation of a medical device and its performance. Misleading or fraudulent advertising of medical devices may increase sales. However, from the buyer's perspective, the purchase of an inappropriate medical device is a waste of money that may deprive the patient of more appropriate treatment and could lead to patient or user injury.

Sale: The sale of medical devices by the vendor is a critical stage that leads to the device being put into actual use. If the vendor is not subject to regulation, then there is a higher risk of exposing the public to low-quality or ineffective devices.

Use: Users of medical devices can have a profound effect on their safety and effective performance. Unfamiliarity with a certain technology or operating procedure, and the use of products for clinical indications outside the scope of those specified in the labeling, can cause device failure even in the absence of any inherent design or manufacturing defects. Within the clinical engineering community, it is widely believed that user error underlies at least half of all medical device-related injuries and deaths. The re-use of disposable devices contrary to the manufacturer's instructions, and without proper control or precautions for minimizing associated risks, can be dangerous. The lack of, or inappropriate, calibration and maintenance of medical devices can seriously jeopardize their safety and performance. These issues are often overlooked or underestimated (11).

Disposal: Disposal of certain types of devices should follow specific and stringent safety rules. For example, devices that are contaminated after use (e.g. syringes) or devices that contain toxic chemicals, can present hazards to people or the environment and must be disposed of properly.

It is people who manage each phase in the life span of a medical device, and these people should be identified and called on to participate in ensuring medical device safety.

MEDICAL DEVICE SAFETY AND RISK MANAGEMENT

The optimum assurance of medical device safety has several essential elements:

- absolute safety cannot be guaranteed
- it is a risk management issue
- it is closely aligned with device effectiveness/performance
- it must be considered throughout the life span of the device
- it requires shared responsibility among the stakeholders

All devices carry a certain degree of risk and could cause problems in specific circumstances. Many medical device problems cannot be detected until extensive market experience is gained. For example, an implantable device may fail in a manner that was not predictable at the time of implantation; the failure may reflect conditions unique to certain patients. For other devices, component failure can also be unpredictable or random. The current approach to device safety is to estimate the potential of a device

becoming a hazard that could result in safety problems and harm. This estimate is often referred to as the risk assessment. Hazard is the potential for an adverse event, a source of danger. Risk is a measure of the combination of (1) the hazard; (2) the likelihood of occurrence of the adverse event; (3) the severity or overall impact. Risk assessment begins with risk analysis to identify all possible hazards, followed by risk evaluation to estimate the risk of each hazard. In general, risk assessment is based on experience, evidence, computation or even guesswork. Risk assessment is complex, as it can be influenced by personal perception and other factors such as cultural background, economic conditions and political climates.

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Cosmetic Devices

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ABBREVIATIONS

EU	European Union
FDA	Food and Drug Administration
GMP	good manufacturing practice
RF	radiofrequency
LED	light-emitting diode
HA	hyaluronic acid
HIFU	high-intensity focused ultrasound
MDA	microdermabrasion

INTRODUCTION

Medical aesthetic devices refer to all medical devices that are used for various cosmetic procedures, which include plastic surgery, unwanted hair removal, excess fat removal, anti-aging, aesthetic implants, skin tightening, etc., that are used for beautification, correction, and improvement of the body. Aesthetic procedures include both surgical and non-surgical procedures. The surgical procedures include liposuction, breast implants, facelifts, radiofrequency, and other related procedures. The non-surgical procedures include chemical peels, non-surgical liposuction, and skin-tightening procedures, among others. Medical aesthetic devices are classified based on types of devices (energy-based aesthetic devices and non-energy-based aesthetic devices) and application (skin resurfacing and tightening, body contouring and cellulite reduction, hair removal, facial aesthetic procedures, breast augmentation, and other applications) (1).

The beauty industry can thank the consumer for continually driving innovation forward due to their insatiable appetite for products that improve the aesthetics of the human body. Some of the developments involve biologically active cosmetics, others more invasive chemical and surgical techniques. An increasing number involve beauty devices, which are oftentimes used in combination with cosmetic products. Device technology can provide the consumer with superior results during their beauty routines, and results that are not always achievable by the use of cosmetics alone.

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Medical aesthetic technology has advanced rapidly over the past two decades in various countries, especially in the United States. The factors that are expected to impact market growth positively include technological advancement in devices, increasing awareness regarding aesthetic procedures, rising adoption of minimally invasive devices, and an increasingly obese population in the region. According to the American Society of Plastic Surgeons, 18.1 million cosmetic procedures were recorded in 2019, an increase of 2% from 2018, which included around 1.8 million cosmetic surgical and 16.3 million cosmetic minimally invasive procedures. The global market for medical aesthetic devices is expected to surpass $8.2 billion by 2024. These devices look to revitalize and tighten skin, soften or reduce wrinkles, and deliver a more youthful appearance. These products are approved by the FDA. The FDA recognizes them as Class II devices if they are electrosurgical, cutting or coagulation devices, or accessories. These products are noninvasive and perform non-surgical tightening of the skin.

Devices that massage, irradiate, or manipulate the skin to alter its structure or function, or underlying tissue, fall into the medical device category. For cosmetic companies venturing into this space, there is a completely different quality paradigm that governs medical devices. Instead of GMP/ISO 22716 for cosmetic products, medical devices adhere to strict ISO 13489 requirements. While there are similarities in these quality systems, there are also substantial differences. The quality management system for medical devices is much more extensive, given the design complexity and risk of these products. Production facilities used for the manufacture of consumer products or cosmetics will be in for a shock should they be required to meet ISO 13489 standards. Even the design of the product will be governed by these strict ISO standards, and the documentation required is enormous.

But before the regulatory and quality system is outlined, a product must first be defined as a drug, medical device, or cosmetic product. Although this may appear simple, it can be challenging as new innovative technologies are created. Cleansing brushes have been popular for many years now. Clarisonic's Mia, for example, claims to lift dirt and oil by oscillating at 300 movements a second to work with the natural elasticity of the skin to remove the impurities. It is classified as a Class I medical device. If a device is to be used in contact with the human body, but its primary function is aesthetic in nature, does that make it a medical device? Something as simple as topical gel is a great example. If the gel is used as a moisturizer, it is considered a cosmetic. However, once it is used for scar reduction, or in an ultrasound procedure, it becomes a medical device. There is a legal distinction between cosmetics and medical devices, and in cases such as this, a highly trained eye is necessary in order to correctly classify and manage newly emerging technologies.

TYPES OF AESTHETIC DEVICES

1. Energy-based aesthetic devices
   i. Laser-based aesthetic devices
   ii. Radiofrequency (RF)-based aesthetic devices
   iii. Light-based aesthetic devices
   iv. Ultrasound aesthetic devices
2. Non-energy-based aesthetic devices
   i. Botulinum toxin
   ii. Dermal fillers and aesthetic threads
   iii. Microdermabrasion
   iv. Implants
      – Facial implants
      – Breast implants
      – Other implants
3. Other aesthetic devices

Dermal Fillers

Aesthetic medicine has advanced greatly in the past decade in terms of our understanding of facial anatomy; the cumulative effects of the aging process; and how dermal fillers may be used to repair, reduce, and even reverse these changes. The four major structural components of the face are skin, fat, muscle, and bone. A reduction in volume in these regions leads to aging. Age-related bone loss in the face can lead to retraction of the jawline, descent of the nose, and loss of high cheekbones. The facial muscles also decrease in volume and elasticity, and the deflation and movement of facial fat further accentuate the signs of aging. Finally, the skin stretches and loses elasticity compounded by the loss of scaffolding provided by fat, muscle, and bone; this leads to wrinkles, sagging skin, and other familiar signs of aging. Dermal fillers help to reduce these sights (2).

Dermal fillers are soft, gel-like substances that are injected under the skin. The areas where dermal fillers are injected are the temporal hollows, cheeks, sub-malar, nose, nasolabial folds, marionette lines, mental crease and lines, oral commissure, and jawline. Most dermal fillers today consist of hyaluronic acid, a naturally occurring polysaccharide that is present in skin and cartilage. Some people may need more than one injection to achieve the wrinkle-smoothing effect. The effect lasts for about six months or longer. Successful results depend on the health of the skin, skill of the health care provider, and type of filler used. Regardless of material (whether synthetic or organic) filler duration is highly dependent on the amount of activity in the region where it is injected. Exercise and high-intensity activities such as manual labor can stimulate blood flow and shorten the lifespan of fillers (3).

Materials used: Fillers are made of sugar molecules or composed of hyaluronic acids, collagens which may come from pigs, cows, cadavers, or the person's own transplanted fat may be generated in a laboratory and biosynthetic polymers. Examples: Calciumhydroxylapatite, polycaprolactone, polymethylmethacrylate, and polylactic acid.

Injection Techniques

A certain amount of practice and experience is required to inject dermal fillers. It is essential to choose the filling agent best suited to each patient and anatomical site, and to determine the appropriate amount of filler to be injected. Another crucial aspect in achieving a good outcome with dermal fillers is the depth at which the material is implanted. Most dermal fillers are injected into the deep dermis or the fatty tissue. A number of different injection techniques are

- Linear threading or tunneling
- Serial puncture
- Radial fanning
- Crosshatching

The filler should be injected deeply. The most common complications are overcorrection and the appearance of lumps, bruises, and localized edema. Only experienced practitioners should undertake this procedure because this is one of the most complicated and delicate treatment areas. Isolated cases of blindness following treatment have been reported, probably caused by poor technique. The likelihood of such a complication can be minimized by administering nerve block anesthesia with epinephrine, which produces vasoconstriction. The recommended technique is to use 30-gauge needles to slowly inject small amounts of filler (4).

Less Common Indications for Dermal Fillers

Scarring

Although no studies in the literature have demonstrated any long-term benefits associated with the treatment of scars with dermal fillers, the injection of HA can improve the patient's appearance, especially in