1

OVERVIEW

JOAQUIM DE CIURANA GAY
Department of Mechanical Engineering and Industrial Construction, University of Girona, Girona, Catalonia, Spain

TUĞRUL ÖZEL
Department of Industrial and Systems Engineering, School of Engineering, Rutgers University, Piscataway, NJ, USA

LIDIA SERENÓ
Department of Mechanical Engineering and Industrial Construction, University of Girona, Girona, Catalonia, Spain

1.1 INTRODUCTION

Medical devices are defined as articles that are intended to be used for medical purposes. Several official definitions exist for the term “medical device” depending on the geographic market. Therefore, medical device definition, classification, and regulation follow market location and governmental regulations according to the required level of control considering invasiveness, contact to the patient, and potential risk in case of misuse or failure. This situation concerning the differences in classification strategies has blocked the spread of innovative medical devices across countries. Nevertheless, in 2011, the International Medical Device Regulators Forum (IMDRF)
was conceived to discuss future directions to harmonize the medical device regulatory field and accelerate international convergence.

Two of the most important medical device markets worldwide are the European and the North American. Therefore, the official definitions and classifications of both regions are detailed in this chapter.

For the European market, medical devices are governed by a regulatory framework of three directives:

- 93/42/EEC: Medical Devices Directive (MDD)
- 90/385/EEC: Active Implantable Medical Device Directive (AIMDD)
- 98/79/EC: In vitro diagnostic medical devices (IVDMD)

According to them, a medical device is defined as “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.”

Similarly, for the North American market and as a part of the Federal Food Drug and Cosmetic Act (FDC 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 which is:

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent on being metabolized for the achievement of any of its primary intended purposes.”

Therefore, any product labeled, promoted, or used in a manner that meets the above-mentioned definition will be regulated by the US Food and Drug
Administration (US FDA) as a medical device and will be subjected to pre- and postmarketing regulatory controls.

Both definitions of medical devices exclude other regulated products such as drugs, the primary intended use of which is achieved through chemical action or by being metabolized by the body, biological products including blood and blood products, or products used with animals.

In order to classify a medical device, the manufacturer should, first of all, decide whether the product concerned is considered a medical device as defined in the previous section. Then, depending on the situation, medical devices can be classified following national or governmental rules. In this chapter, the classification given is based on the European Union (EU) and the US FDA regulations.

According to the EU, the classification of medical devices is based on the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways and be applied to a vast range of different medical devices and technologies. These criteria are referred to as the “classification rules” and are described in Annex IX of Directive 93/42/EEC. Therefore, the medical device manufacturer must determine the type of device following the rules listed in Annex IX. The rules depend on a series of factors including

- **duration**: how long the device is intended to be in continuous use,
- **invasiveness**: whether or not the device is invasive or surgically invasive,
- **type**: whether the device is implantable or active,
- **function**: whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device,

and are divided as follows:

- **Rules 1–4**: for noninvasive devices,
- **Rules 5–8**: for invasive devices,
- **Rules 9–12**: for active devices,
- **Rules 13–18**: special rules for products that merit a higher classification than they might otherwise be assigned.

When multiple rules apply, the manufacturer must use the highest risk class. Nevertheless, a small number of products may be more difficult to classify due to their unusual nature or situations where the classification would result in the wrong level of conformity assessment in light of the hazard represented by the devices.

Furthermore, based on these rules described in Directive 93/42/EEC, the devices are divided into four classes, ranging from low risk to high risk:

- **Class I**: low-risk medical devices,
- **Class IIa**: medium-risk medical devices,
- **Class IIb**: medium-risk medical devices,
- **Class III**: high-risk medical devices.

Thus, in order to classify a medical device, the manufacturer must determine the classification of the medical device (class I, class IIa, class IIb, or class III) considering the Annex IX rules described later. Then, a notified body has to carry out the appropriate conformity assessment procedure to validate and confirm the classification.

As an example, a manufacturer willing to classify a silicone tracheal stent must consider the rules associated with an invasive medical device (Rules 5–8):

- **Rule 5** *(invasive in body orifice or stoma—not surgically)*

  - If it is for transient use Class I
  - If it is for short-term use Class IIa
  - *However*, if it is for oral cavity, ear canal, or nasal cavity Class I
  - If it is for long-term use Class IIb
  - *However*, if it is for oral cavity, ear canal, or nasal cavity and it will not be absorbed by the mucous membrane Class IIa
  - If it is connected to an active medical device in class IIa or higher Class IIa

- **Rule 6** *(surgically invasive—transient use)*

  - If it is surgically invasive for transient use Class IIa
  - If it is used to control/diagnose/monitor/correct a defect of the heart or the central circulatory system through direct contact Class III
  - If it is used for the central nervous system (direct contact) Class III
  - If it is a reusable surgical instrument Class I
  - If it is used to supply energy or ionizing radiation Class IIb
  - If it has a biological effect (mainly or wholly absorbed) Class IIb
  - If it is intended to administer medicines in a potentially hazardous manner Class IIb

- **Rule 7** *(surgically invasive—short-term use)*

  - If it is surgically invasive for short-term use Class IIa
  - If it is used to control/diagnose/monitor/correct a defect of the heart or the central circulatory system through direct contact Class III
  - If it is used for the central nervous system (direct contact) Class III
  - If it is used to supply energy or ionizing radiation Class IIb
  - If it has a biological effect (mainly absorbed) Class III
  - If it undergoes chemical changes in the body, or if it administers medicines (not in teeth) Class IIb
• **Rule 8** (*surgically invasive—long-term use or implantable devices*)

If it is surgically invasive for long-term use or if it is an implantable device
Class IIb
If it has to be placed in teeth
Class IIa
If it has to be in contact with the heart or central circulatory/nervous system
Class III
If it has a biological effect (or mainly absorbed)
Class III
If it undergoes chemical changes in the body, or if it administers medicines (not in teeth)
Class III
For specific derogation: breast implants, hip, knee, and shoulder joint replacements
Class III

Specifically for the example, the manufacturer must consider the following:

• **Duration:** the silicone stent will be placed inside the trachea for more than 30 day; therefore, the device is for long-term use (**Rule 8**).

• **Invasiveness:** the stent will be totally introduced inside the orifice of the trachea using a bronchoscope and anesthesia (surgical operation); therefore, the device is considered an implantable device (**Rule 8**).

Taking these considerations into account, a simple silicone tracheal stent must be considered a class IIb medical device, because it is a long-term implantable device not placed in teeth, without contact with the circulatory or nervous system, without a biological effect, which does not undergo chemical changes or administers medicine, and it is not a breast implant or a hip, knee, or shoulder joint replacement.

**US Medical device classification**, as in Europe, depends on the intended use of the device and also on indications for use. Moreover, classification is based on the risk the device poses to the patient and/or the user. There are several factors that may affect the risk including

• the design of the medical device, which should include principles of inherent safety,
• the manufacturing process, which must be well planned, under control, and validated,
• the intended use, which will define the adequate scope of use excluding other places where the medical device is not intended for use,
• the identification of the user, defining its expected experience, education, and training,
• the safety or health of users, implying that the medical device should not compromise the safety of patients.

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.
The US FDA has established a classification of approximately 1700 generic types of medical devices grouping them in the CFR into several medical specialties referred to as panels:

<table>
<thead>
<tr>
<th>Medical Specialty</th>
<th>Regulation Citation (21 CFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 Anesthesiology</td>
<td>Part 868</td>
</tr>
<tr>
<td>74 Cardiovascular</td>
<td>Part 870</td>
</tr>
<tr>
<td>75 Chemistry</td>
<td>Part 862</td>
</tr>
<tr>
<td>76 Dental</td>
<td>Part 872</td>
</tr>
<tr>
<td>77 Ear, nose, and throat</td>
<td>Part 874</td>
</tr>
<tr>
<td>78 Gastroenterology and urology</td>
<td>Part 876</td>
</tr>
<tr>
<td>79 General and plastic surgery</td>
<td>Part 878</td>
</tr>
<tr>
<td>80 General hospital</td>
<td>Part 880</td>
</tr>
<tr>
<td>81 Hematology</td>
<td>Part 864</td>
</tr>
<tr>
<td>82 Immunology</td>
<td>Part 866</td>
</tr>
<tr>
<td>83 Microbiology</td>
<td>Part 882</td>
</tr>
<tr>
<td>84 Neurology</td>
<td>Part 884</td>
</tr>
<tr>
<td>85 Obstetrical and gynecological</td>
<td>Part 886</td>
</tr>
<tr>
<td>86 Ophthalmic</td>
<td>Part 888</td>
</tr>
<tr>
<td>87 Orthopedic</td>
<td>Part 864</td>
</tr>
<tr>
<td>88 Pathology</td>
<td>Part 890</td>
</tr>
<tr>
<td>89 Physical medicine</td>
<td>Part 892</td>
</tr>
<tr>
<td>90 Radiology</td>
<td>Part 862</td>
</tr>
<tr>
<td>91 Toxicology</td>
<td>Part 868</td>
</tr>
</tbody>
</table>

For each of the devices classified by the US FDA, the CFR gives a general description including the intended use, the class to which the device belongs, and information about marketing requirements. Therefore, the panel examines and classifies the device in three different classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device:

1. **Class I (Low Risk)—General Controls:**
   (a) FDC Act lists general references to control the medical devices.
   (b) Some general controls include the following: the device cannot be adulterated or misbranded; the firm must be registered with the US FDA, must maintain records and reports, and must apply good manufacturing practices, etc.

2. **Class II (Medium Risk)—Special Controls:**
   (a) For those devices, general controls are not sufficient; therefore, special controls are set.
   (b) Special controls include performance standards; postmarket surveillance; patient registries; guidelines; etc.
3. **Class III (High Risk)—Premarket Approval:**
   
   (a) For those devices, general and special controls are not sufficient; therefore, premarket approval is needed.

   (b) Applications for premarket approval include reports about the safety and effectiveness of the device; a statement of components, properties, and elements of the device; description of the methods, manufacturing controls, packing; references to any relevant standard; sample of the device and components; proposed labeling; certification related to clinical trials; etc.

Thus, the class to which the medical device is assigned determines, among other things, the type of premarketing submission/application required for US FDA clearance to market. However, there are exceptions and exemptions for certain devices.

### 1.2 NEED FOR MEDICAL DEVICES

Medical devices are indispensable for effective prevention, diagnosis, treatment, and rehabilitation of illness and disease. They help to not only save and prolong life but also improve the quality of life. Therefore, identifying diseases, disabilities, and risk factors is a decisive step to develop new and efficient medical devices. However, besides medical and technological attributes, the development of medical devices is often influenced by other considerations such as markets, costs, and physician preferences.

Nowadays, there are more than 1.5 million different medical devices, including thermometers, surgical drapes, pacemakers, infusion pumps, heart-lung machines, dialysis machines, artificial organs, implants, prostheses, corrective lenses, etc. Currently, orthopedic implants make up the bulk of all devices implanted (~1.5 million per annum worldwide) at a cost of around $10 billion. However, innovation will continuously serve as the fuel for market growth, bringing disruptive products and technologies to market.

New discoveries in biomaterials, technologies, computing, and biology will generate knowledge and growth of new treatments and cures, driving the medical device market to more cost-effective and patient-centered solutions.

Biomaterials are extremely linked to the performance of medical devices, and therefore, to the quality of life of patients. The definition of biomaterials has changed over time [1, 2] while several generations have been developed. However, these generations should be interpreted as the evolution of the requirements and properties of the medical devices. We can group them as follows:

- **Inert Biomaterials:** During the 1960s and 1970s, a first generation of biomaterials was developed for implantation and generation of medical devices. The goal of these inert biomaterials was to replace damaged tissue and provide structural support with a minimal tissue response in the host [3].
• **Bioactive Biomaterials:** In the 1980s and 1990s, a second generation of biomaterials, which was able to elicit a specific biological response at the interface of the material, began to develop. The bioactivity was accomplished by using coatings or similar strategies in order to increase and improve implant lifetime by optimizing the interface with the host tissue. These bioactive materials allowed the creation of more effective and less invasive medical devices [4–6]. Nowadays, this type of biomaterials is still used in many commercial products, for example, in dentistry and orthopedics [7].

• **Biodegradable Biomaterials:** Besides the advantages of bioactive materials, long-term implants were generally associated with infections, reactions due to toxicity or immunological processes, mechanical implant failure due to fatigue, etc. As a consequence, a third generation of biomaterials was developed. These biomaterials have the capability to degrade and be absorbed offering the possibility to overcome the drawbacks of permanent implants [3].

• **Smart Biomaterials:** Progress in biology, proteomics, and bioengineering during the last decade has led to the development of a fourth generation of biomaterials [8–12]. Smart biomaterials are willing to mimic nature’s hierarchical structures and mechanisms to actively repair and regenerate damaged tissue by stimulating specific cellular responses. However, the re-creation of the tissue extracellular matrix is complicated and represents one of the challenges of the biomaterials field. However, important progress has been made in the design and manufacturing of scaffolds for tissue engineering and regenerative medicine. Nevertheless, despite their considerable advantages, only few smart biomaterials are being used for clinical applications so far.

While the first generation of biomaterials is still used in a wide range of applications, smart biomaterials will open innovative and new possibilities of treatments and applications.

Concerning the type of material, the vast majority of medical devices (stents, orthopedic implants, bone fixators, artificial joints, etc.) are made of metallic materials due to their strength, toughness, and durability. An extensive review on this topic has been done by Hanawa [13]. Specifically, metals have high strength, high elasticity, high fracture toughness, and high electrical conductivity when compared with ceramics and polymers. However, improvements of corrosion resistance and mechanical durability are needed in order to avoid environmental and health concerns over heavy metals used for medical purposes. In this context, there is a need to research and improve mechanical and surface properties of metals, because these features are key to tissue compatibility. Therefore, their physical properties (mechanical, biodegradable, magnetic, etc.) must be improved by redesigning metallic alloys and biofunctionalizing their surface.

Titanium alloys, such as Ti-6Al-7V, Ti-6Al-7Nb, Ti-6Al-2.5Fe, Ti-13Zr-13Ta, Ti-6Al-2Nb-1Ta, and Ti-15Zr-4Nb-4Ta, have been widely used for medical and dental applications. This type of $\alpha + \beta$ titanium alloy shows high corrosion resistance, specific strength, and good tissue compatibility. Because of their Young’s modulus and corrosion resistance, titanium alloys are preferred over stainless steel.
and cobalt-chromium alloys for orthopedic and dental applications. However, their low elongation is often associated with fractures. Thus, the development of $\alpha + \beta$ titanium alloys with high elongation and sufficient strength is needed because no optimal titanium alloy is available so far. In addition, Young’s modulus of metallic materials is still higher than cortical bone, inducing stress shielding and fracture. To solve these problems, metals with lower Young’s modulus are needed. Several $\beta$-type titanium alloys with a low Young’s modulus, including Ti-12Mo-6Zr-2Fe, T-15Mo, and Ti-15Mo-5Zr-2Al, have been developed for this purpose [14, 15]. On the other hand, ultrahigh-molecular-weight polyethylene and poly(methyl methacrylate) are being used to fill porous titanium alloys in order to obtain materials with reduced Young’s modulus [16, 17].

Titanium-nickel alloys have been used to manufacture various medical devices, such as stents, guide wires, and endodontic reamers, due to their specific mechanical properties (shape memory, superelasticity, and damping). Nevertheless, material fractures, pitting, and crevice corrosion have been recently reported [18–21]. In fact, there is a significant problem of toxicity and allergy due to the release of nickel ions. Thus, alloys with better corrosion and fatigue properties must be developed. In fact, there is a huge demand for developing superelastic and shape-memory alloys without using nickel. Some alloys, such as Ti-Sn-Nb, Ti-Mo-Sn, Ti-Nb-O, and Ti-Nb-Al, have been produced with good shape-memory but not enough recovery strain and superelastic deformation stress. On the other hand, nickel-free austenitic stainless steel materials are being developed to obtain materials with better corrosion resistance and strength for medical purposes. Some examples are Fe-(19-23)Cr-(21-24) Mn-(0.5-1.5)Mo-(0.85-1.1)N alloy (BioDur® 108), Fe-18Cr-18Mn-2Mo-0.9N alloy, and the Fe-(15-18)Cr-(10-12)Mn-(3-6)Mo-0.9N alloy. Co-Cr alloys exhibit excellent corrosion resistance and good wear resistance. However, when using these alloys as orthopedic prosthesis, they produce stress shielding in the adjacent bone. The lack of mechanical stimuli on the bone may lead to the failure and loosening of the implant due to bone resorption. Therefore, osseointegration is another relevant requirement for metallic implantable devices. To solve this problem, there is a need to develop techniques and methodologies to modify their surface in order to give them biofunctionality and improve tissue compatibility. This requirement is currently being fulfilled by using dry and wet processes, which are the most conventional and predominant surface modification techniques [22, 23]. Research in this field is ongoing for techniques that involve the immobilization of biofunctional molecules. However, due to difficulties in ensuring appropriate safety, quality, and durability of those treatments, these are still not used commercially. Further research is needed in order to study the biofunctionalization of metallic materials to use them in innovative technologies such as tissue engineering.

Another important requirement for some medical devices is the ability to be absorbed by the body. This feature is typical of some polymeric materials, but not metallic ones. In fact, there are two metallic materials that should be considered bioabsorbable: iron and magnesium. However, strict control of corrosion rates must be achieved for biodegradable magnesium alloys due to a certain degree of late recoil and neointima formation.
Metallic materials, such as stainless steels, Co-Cr alloys, and titanium alloys, become magnetized when a magnetic field is applied inducing the appearance of artifacts and the disablement of the magnetic resonance imaging (MRI) diagnostic tool. Since this is an important and widely used diagnostic tool, there is a need to develop medical devices made of materials with low magnetic susceptibility. In this sense, materials such as Au-Pt-Nb, Ti-Zr, Zr-Nb, and Zr-Mo alloys are being proposed due to their reduced magnetic susceptibility compared with other material such as Co-Cr-Mo and Ti alloys [24, 25]. However, some of them are difficult to process because of their tensile strength and elongation rates.

Alumina, zirconia, and porous ceramics are commonly employed to develop implantable medical devices such as femoral heads and hip prostheses. Their microstructure depends on the manufacturing system employed and is proportional to the mechanical and biological properties. Ceramic biomaterials show good wear rates, corrosion resistance, biocompatibility, and high strength [7]. Nevertheless, there is a need to increase the quality of ceramic materials to improve their low fracture toughness. On the other hand, porous ceramics (e.g., hydroxyapatite) used to mimic trabecular bone are exposed to mechanical collapse risk, and also their compression strength can be affected by aging. Bioactive ceramics, such as bioactive glasses (BGs), glass-ceramics, and calcium phosphates (CaPs), have been used as bone substitutes for decades due to their similitude with bone mineral structure. However, owing to their low tensile strength, poor mechanical properties, and low fracture toughness, they cannot be used for load-bearing applications. Further studies are needed to improve the mechanical features of these kinds of ceramic materials.

On the other hand, the use of polymers in surgery, prosthetics, pharmacology, and drug delivery is essential. Many polymeric compounds are considered biomaterials and used in many applications: silicones (tubes, plastic surgery), polyurethanes (catheters, cardiac pumps), polytetrafluoroethylene (orthopedics), nylon-type polyamides (sutures), polymeric compounds based on methyl methacrylate (cements, odontology, prostheses), etc. However, there is a need to improve their biostability and performance in terms of clinical applications because the release of wear debris is often present in those materials leading to undesirable effects.

Many medical devices are implanted in the body and a second surgical procedure is often required to remove the remnants of a previous implant. In this regard, the use of biodegradable polymers has been the key [26]. Moreover, their flexibility, durability, and biocompatibility have made them very important to develop safety devices such as orthopedic implants, sutures, drug eluting stents, and scaffolds. Moreover, biodegradable polymers can reduce the stress shielding effect, avoid removal of implants, and enable postoperative diagnostic imaging. Biodegradable polymers can be classified as synthetic and natural. Synthetic polymers are able to be hydrolyzed by human tissues. Some examples are polylactic acid (PLA), polyglycolic acid (PGA), poly-ε-caprolactone (PCL), polyethylene glycol (PEG), etc. [27]. Natural biodegradable polymers are proteins or polysaccharides (chitosan, agarose, collagen, alginate, etc.), which undergo enzymatic degradation. The mechanisms of polymeric degradations are bulk erosion and surface erosion. The understanding of these mechanisms is crucial to design and develop safe and efficient smart devices, drug delivery devices,
scaffolds, or bioactive products. From a mechanical point of view, these types of polymers can be reinforced using oriented fibers or fibrils of the same material. This strategy provides these materials with fair mechanical properties.

Another type of frequently used polymeric material for medical device applications is silicone. Silicones have unique properties, such as biocompatibility, biodurability, chemical and thermal stability, hydrophobicity, and low surface tension, which allow them to be extensively used in the medical field. Silicones have been used to manufacture orthopedic implants, catheters, drains, shunts, medical machines, valves, esthetic implants, stents, to name just a few. However, there are some concerns about the biocompatibility and biodurability of silicones that have recently been under discussion. Some silicone materials have not passed the biocompatibility tests, and their purity is not suitable for medical purposes. On the other hand, notwithstanding silicones’ chemical stability, certain factors may affect its durability and long-term performance.

Based on clinical experience, there are several biological, mechanical, chemical, and physical requirements for biomaterials that should be targeted to develop more efficient and adequate medical devices including foreign body reaction (due to wear fibrils), stress shielding, biocompatibility, bioactivity, osteoinduction, etc. A description of the major requirements is listed here:

- **Safety:** it is the most important requirement for medical devices. They must be safe and not show any toxicity. Therefore, corrosion-resistant materials should be used.
- **Durability:** there is a need to improve the durability of materials and wear resistance in order to increase product life and reduce medical interventions due to replacement or fatigue problems.
- **Mechanical Compatibility:** this is a key characteristic for multiple purposes such as to avoid stress shielding.
- **Biodegradability:** in order to increase biocompatibility, reduce immune reactions, and avoid retrieval, there is a need to develop biodegradable materials.
- **Biofunction:** to improve the performance of several medical devices, there is a need to promote bone formation (e.g., fixation of devices in bone), to promote adhesion of soft tissue (e.g., fixation of soft tissue), to prevent thrombus (e.g., inhibition of platelet adhesion), to avoid infections (e.g., inhibition of biofilm formation), to reduce magnetic susceptibility (e.g., avoid artifacts in MRI), etc.

Finally, a major concern in the medical device field is infection. Bacteria often colonize the surface of medical devices developing a biofilm that compromises not only the functionality and performance of the device but also the patient’s health. For these cases, removal of the infected device is frequently the only option. Therefore, a solution for septic failures must be considered as a real need due to the high morbidity and enormous costs associated. Currently, there is no specific approach that can ensure the development of medical devices exempt from possible infections. Even sterile procedures, antibiotic prophylaxis, and appropriate aseptic management
of the devices do not guarantee obtaining a resistant device. However, along with preventive measures, the use of biomaterials with a certain degree of bacterial resistance is being applied. There are many materials, such as noble metals, that have bactericidal properties. With the development of new medical devices, an increased number of anti-infective biomaterials has arisen. Biomaterials have been formulated to release antibacterial, antifungal, antiviral, antiprotozoal, and anthelmintic drugs. And even to treat other types of pathogens. The vast majority of anti-infective biomaterials are the ones with antibacterial properties [28]. Some of the most broadly used medical devices, such as contact lenses and catheters, are extremely exposed to those infections. However, the potential risk of infection is based on the degree of invasiveness of each medical device. Thus, the strategy to determine the most suitable anti-infective device should take it into account. Whether we have external medical devices, partially internal medical devices, or a totally internal medical devices will determine the type of possible infections and the characteristics of the process. Future strategies should focus on designing and developing biomaterials with specific and appropriate anti-infective properties for each application.

The complexity of new biomaterials demands to develop specific and efficient manufacturing technologies. Current needs in biomaterials and technologies should pursue the goal of enhancing tissue regeneration rather than replacement. To address this need, several strategies are being explored including surface modification, development of drug delivery systems, generation of advanced three-dimensional scaffolding geometries for tissue engineering, etc. Moreover, some researchers are willing to develop smart materials with intrinsic ability to enhance and promote the capacity of the damaged tissue to self-repair and regenerate by stimulating cellular migration, attachment, and proliferation, as well as vascularization and nutrient supply [29–33]. These capabilities can be imparted to biomaterials by using technologies that allow modifying or regulating some surface characteristics (e.g., roughness), morphological properties (e.g., porosity), degradation mechanisms, and mechanical features. Nevertheless, besides the progress made in the field, a major barrier to promote this innovation is the low rate of commercially available smart medical devices.

1.3 TECHNOLOGY CONTRIBUTION TO MEDICAL DEVICES

Design and manufacturing of medical devices is essential to improve patients’ quality of life and treatment effectiveness while reducing health-care costs. Owing to the nature of these devices, the requirements to develop medical devices include biocompatibility, reliability, corrosion resistance, controllability, and customization among others. Currently, conventional technologies are being used to obtain marketable products; however, advanced manufacturing technologies are required to achieve innovative medical devices with desired results.

To meet the challenges of new medical devices, the term Biomanufacturing has been addressed. Biomanufacturing was defined as the application of design and manufacturing technologies to reduce the cost while advancing the safety, quality, efficiency, and speed of health-care service and biomedical science [34]. The term
includes several fields of study such as design, mechatronics, fabrication, and assembly.

The technology contribution to medical devices is based on the combination of a good understanding and availability of materials and fabrication processes. Some requirements should be first addressed, such as, biocompatibility and corrosion/fatigue resistance. For this reason, the election of an appropriate material and manufacturing technology is very important.

A new set of manufacturing technologies emerged in the past decades to address market requirements such as the need to develop customized low-cost medical devices. These new technologies are usually referred to as rapid prototyping [35]. Rapid prototyping (RP), developed around the mid-1980s, enables the production of useful prototypes to test the fit, form, and function of medical devices prior to their release to the market. Nowadays, these technologies have evolved to rapid manufacturing (RM) and are able to produce directly functional parts and products. In addition, RP is also useful to create models to plan and prepare surgical approaches or to train medical students.

The medical device manufacturing technologies can be classified into subtractive, net-shape, and additive processes. A brief description of some of these technologies is given in the following sections. More detailed information is presented in the following chapters.

1.3.1 Subtractive Technologies

The progress in medical devices based on new technologies is often transferred from other industries to the medical field. Within subtractive technologies, we find mechanical (turning, milling, drilling, and grinding), electric (EDM), electronic beam, and chemical processes. All of them have been used to manufacture a broad variety of medical devices.

Machining technologies have been used to manufacture some medical devices. In particular, laser micromachining has been widely used to produce vascular stents [36]. A stent is a tubular wire mesh that is deployed in a diseased coronary artery to provide a smooth blood circulation [37]. Recently, the emergence of fiber laser technologies has enabled their increasing applications in medical device micromachining. In laser machining, device fabrication is performed by incremental removal of material using a laser. However, ablation of material cannot take place at locations where the laser path is obstructed. Therefore, this constraint limits the geometries that can be fabricated by laser machining, such as structures with overhangs or interior geometries [38]. Other applications of laser machining are the production of scaffolds for tissue engineering and channels for microfluidic devices [39, 40].

1.3.2 Net-Shape Technologies

Forming and molding are used for large-scale production. In the case of medical device production, for example, pacemakers and electronic connections are made using forming processes, while hearing aid devices are molded. For small batches
or single products, a new process has been recently used: incremental sheet forming (ISF) [41, 42]. Due to the natural difference between individuals and treatments, incremental forming technologies can also be applied to develop new medical devices. This process will allow high customization with affordable costs. Thus, research has been focused on increasing the geometric accuracy [43–45], geometric flexibility [46, 47], and exploring new applications [48–50].

1.3.3 Additive Technologies

Over the past decades, additive technologies have been used to produce medical devices from CAD models based on computed tomography (CT), MRI, and other medical imaging techniques [51–53]. In fact, the number of applications for these technologies in the medical area is increasing. The basic concept of additive manufacture is the fabrication of a 3D model by adding consecutive layers. The main advantage of this technique is the capacity to rapidly produce very complex 3D models and the ability to use various raw materials. Using additive technologies, it is possible to obtain customized devices with specific geometry, size, and function for a given patient and a given medical context. In addition, surgeons can use additive processes to fabricate exact anatomical replicas for surgical planning or training. Additive processes can be divided in electrochemical processes and physical processes.

1.3.3.1 Electrospinning Electrospinning uses an electrostatically driven jet of polymer solution to produce micro- or nano-fibers. These fibers can be used to produce nanostructures for tissue engineering [54–58].

1.3.3.2 Stereolithography Stereolithography (SLA) is an additive process used to produce 3D objects through curing a photoreactive resin with a power source [59–61]. Excitation of photoreactive molecules, formation of reactive species, generation of free radicals, and polymerization of the resin occurs in the region of laser-resin interaction. Two distinct methods are usually employed in this process: mask-based method and UV beam method. In the former, an image is transferred to a liquid polymer by irradiation through a patterned mask, while in the latter, a UV beam is focused to selectively solidify the liquid resin. SLA is used to produce surgical guides for the placement of dental implants, temporary crowns and bridges, and resin models for lost wax casting, among others [62]. SLA of biodegradable polymers has also been used to produce tissue engineering scaffolds [63,64]. Several clinically implanted prostheses, including auricular, maxillofacial, and cranial prostheses, have been obtained using this technology [65–67], as well as hydroxyapatite (HA) ceramic scaffolds for orbital floor prosthesis [68].

1.3.3.3 Extrusion-Based Techniques The extrusion-based technique is commercially known as fused deposition modeling (FDM). This process was developed by Crump and marketed by Stratasys Corporation [69]. In this process, a thin filament of plastic material is melted and extruded through an extrusion head, which deposits
the filament layer by layer to produce a final part. This FDM process is limited to available thermoplastic materials that may be formed into filaments, heated, and deposited. However, they have been used to produce parts from medical-grade materials. Nowadays, the use of FDM to produce permanent implants has been limited to the fabrication of models that can serve as templates for the fabrication of custom implants [70]. On the other hand, extrusion-based processes (bioextrusion) are widely used to produce scaffolds for tissue engineering.

Another extrusion-based technique has appeared recently. The multi-phase jet solidification (MJS) is based on the extrusion of metal or ceramic slurries using the metal injection molding technique. The main difference between this technique and the FDM lies in the raw material and the feeding system [71].

1.3.3.4 Inkjet Printing  Inkjet printing deposits tiny droplets of material onto the required locations to form layer by layer a 3D object. The material is a mixture of the raw material with a binder, which is removed later. Inkjet printing comprises two configurations: the bonder method and the direct build-up method. The most common application of inkjet printing is the production of prototypes for form and fit testing. However, other medical devices are being produced using this kind of technology, including MEMS, drug eluting devices, scaffolds, and artificial tissues and organs.

1.3.3.5 Laser Sintering and Melting  Selective laser sintering (SLS) and selective laser melting (SLM) are additive manufacturing processes that use high-energy light sources to consolidate powder material [72–75]. Both technologies have been used to produce permanent and temporary implants [76].

1.3.3.6 Electron Beam Melting  Electron beam melting (EBM) is an additive manufacturing process that uses an electron beam to scan a layer of metal powder on a substrate, forming a melt pool [77, 78]. The system consists of the electron beam gun compartment and the specimen-fabrication compartment both kept in a high vacuum. EBM has been used to produce titanium root-form implants (Ti-6Al-4V ELI) [79], femur-hip implants [80], dental implants [77], and knee replacement implants [81].

Additive manufacturing (AM) technologies, as an evolution of rapid prototyping methods, can produce direct products satisfying mechanical, physical, chemical, and biological requirements.

In the medical area, AM are playing a key role due to its capability to reproduce complex shapes and geometries impossible to be produced using other manufacturing processes. There are many research works showing how additive technologies can produce difficult shapes, adjust process parameters, or check mechanical capabilities [82]. In general, research is focused on additive manufacturing technologies performance using different technologies and different materials. Chimento et al. [83] evaluated the performance of 3D printed materials for use as rapid tooling (RT) moulds in low-volume thermoforming processes such as in manufacturing custom prosthetics and orthotics.
1.4 CHALLENGES IN THE MEDICAL DEVICE INDUSTRY

The aging of the population, the need to have a good quality of life, and altogether the scientific and technological progress represent an immense potential for the medical device market. This situation creates an ideal environment for the emergence of new challenges and opportunities. In this section, some challenges of the medical devices industry are explained.

- Innovation in the medical device market implies improving the quality of treatment, considering the quality of established treatment options (e.g., reduce morbidity and mortality, reduce pain, increase implant survival, etc.), while improving the costs of the treatment, considering the direct and indirect costs of the established treatments. Innovation seeks a beneficial effect in both pillars, increasing quality while simultaneously decreasing costs. However, many recently developed smart medical devices increase costs, mainly due to the enormous associated technological knowledge. Consequently, one major challenge is to develop appropriate industrial technologies and processes capable of producing reproducible, safe, effective, and economically acceptable medical devices.

- Due to the globalization of the markets, health-care providers are exploring new opportunities in developing nations in order to increase efficiencies and reduce costs. According to the United Nations, there are approximately 5 billion people living in low-resource developing countries, while only 1.2 billion live in high-resource developed nations. This means that the potential market in developing countries is enormous, generating new opportunities for lower production costs. Therefore, a challenge of the medical device industry is to explore and exploit this market by exporting medical devices or directly establishing manufacturing facilities in low-income countries. However, companies must pay attention to maintaining workers’ rights and ethical issues.

- Important challenges are associated with medical devices’ policies and regulations. New strategies need to be developed to handle the generation of new medical devices such as regenerative medical devices (scaffolds) and drug-eluting medical devices among others. Nevertheless, it is essential for the collaboration of all stakeholders (medical device industry, governments, academia, NGOs, professionals, etc.) to share knowledge and expertise in order to determine specific and required actions to increase the quality, effectiveness, and coverage of health-care policies and regulations.

- Personalized or customized treatments have proven to be more efficient, effective, and safe in many cases. Although the generation of customized products is a hot topic in the biomedical research area, its application in the market is very limited due to regulatory and practical reasons. Nowadays, the design and manufacturing of medical devices are subject to national and international policies and regulations that require clinical trials to validate their efficacy and safety. Therefore, any deviation concerning the design, materials, or manufacturing
procedures require extensive studies and tests to be re-approved. This is a clear barrier against the generation of customized medical devices and represents a challenge to overcome in order to produce more suitable and efficient products and treatments.

- A current focus of research is the development of smart medical devices. Smart medical devices are made of bioinspired materials able to reproduce the function of the tissue or body part that they are replacing or assisting. They have complex and multifunctional structures that can integrate multiple chemical inputs and physical stimuli that determine their behavior. Such devices could target desired anatomical regions or specific cellular populations, making it a very effective treatment with minimal side effects. The study and generation of these devices and biomaterials is both a challenge and a need. The understanding of biological processes, the creation of new biomaterials, and the development of innovative technologies are a requirement to create devices for diagnostic or therapeutic applications.

- Allografts, autografts, and xenografts are currently being used to replace damaged tissue. Nevertheless, there are several limitations associated with them, such as scarcity, rejection, disease transfer, harvesting costs, and postoperative morbidity to name a few [84–86]. In those situations, tissue engineering or regenerative medicine have emerged as an effective and adequate alternative to overcome these problems. Tissue engineering is based on the use of scaffolds combined with natural components (e.g., cells, growth factors, molecules, etc.) and signaling pathways to repair and regenerate organs and tissues [87]. Although there are many research areas exploring and studying tissue engineering, its implementation as a routine treatment is still controversial. A significant challenge to solve is the angiogenesis, which is crucial to stimulate tissue regeneration after implantation. In addition, the manipulation of these structures, such as the scaffolds with cells, represents an additional complication for their widespread use in hospitals.

REFERENCES


