Medical devices specificities: opportunities for a dedicated product development methodology

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Summary

The medical sector, similarly to other industries as the aviation industry, has to comply with multiple regulations, guidelines and standards. In addition, there are multiple definitions for the expression ‘medical device’ and, before entering the market, manufacturers must demonstrate their product’s safety and effectiveness. In such a complex and demanding environment it is crucial to know the particularities surrounding the product being developed in order to minimize the chances of a commercial flop. Thus, in this paper, the medical device’s specificities are identified and the most relevant legislation is reviewed providing the foundations for a dedicated product development methodology.

Keywords

Medical device characteristics, regulations, standards, product regulatory approval, Europe, USA, Global Harmonization Task Force

Expert commentary

The medical device industry is young and is in continuous growth. However, this growth is threatened by the same features that make the sector unique. Most companies start when academics realize that the medical problem they were trying to solve has a commercial potential; by that time, they also realize that the characteristics of medical devices have been neglected and, in order to commercialize their product, the development process has to be repeated but this time complying with the multiple standards and regulations.
Among academics the product development methodology applied to medical devices is a novelty and there is interest in a tutorial. In order to design such a tutorial it is important to identify the unique characteristics of medical devices.

**Five-year view**

In the early 1990s, efforts started being gathered to achieve greater uniformity between national regulatory systems for medical devices. Nearly two decades later, little has change. In the near future, changes are not expected. Thus, the development of medical devices will have to adapt to the existing reality. Both companies and academics will have to learn what makes the sector peculiar and join efforts to design methodologies that facilitate the development of medical devices more efficient.

Product development methodologies are not new, but few are dedicated to medical devices. Currently there are some books about 6 sigma and design for X in the medical device industry. However, this number is expected to increase in the near future as people realize that the current methods are inefficient.

**Key issues**

- Overall, ‘medical device’ refers to any item intended to be used in the diagnosis, prevention, monitoring, treatment or alleviation of a disease or an injury. It encompasses various devices from wooden tongue depressors to sophisticated diagnostic equipment.
- Medical devices are classified according to the level of risk that they pose affecting their path to market as well as the degree of care in their utilization.
- Medical devices are regulated products and, as such, regulation affects the industry’s performance.
- The industry of medical devices is dynamic and is in constant growth.
- After market introduction, medical devices continue to be evaluated in order to assess their safety and effectiveness affecting coverage and reimbursement.
- The industry of medical devices is complex and justifies a dedicated product development methodology.

**Introduction**

Medical devices have existed since prehistoric times; in fact, surgical instruments used in cranial trepanations were found at Neolithic excavation sites and there are proofs of the use of acupuncture needles in prehistoric Peruvian mummies [1]. The Greeks and the Romans developed numerous devices similar to the ones used today, namely dilators and tweezers, and, in the Middle Ages, many other devices were created. The modern medical technology began in the mid-19th century with the invention of the ophthalmoscope and the laryngoscope and later on with the discovery of x-rays [2]. According to the World Health Organization (WHO), currently there are around 1.5 million different medical devices [3]. At first glance, this number is overwhelming but, considering that the term ‘medical device’ includes apparatuses ranging from simple wooden tongue depressors to drug-eluting stents or engineered tissues, the figure becomes reasonable.
As far as complexity is concerned, the medical device industry is similar to the aviation or nuclear sectors. The multiple definitions for the expression ‘medical device’ along with the multiplicity of regulations and standards that the devices must comply with and the existence of motley agencies that evaluate the devices before commercialization are a clear indicator of the sector’s intricateness. In this paper, the characteristics that make the medical device industry peculiar are presented in order to help manufacturers, designers and physicians and even patients to better understand what defines a medical device and the process by which they are evaluated and approved for use. Furthermore, as literature regarding medical devices, namely their specificities and development methodologies, is scarce, this paper intents to help manufacturers including designers to tackle the complexities of the medical device industry.

The information presented here was scattered in several web pages, peer-reviewed journals, books, standards and regulations, and is organized as follows. After the presentation of common definitions for the expression ‘medical device’, the regulatory framework is described as well as the device’s multiple classifications. Then, the commercialization process in Europe and the USA is explained and an overview of the market and post-market surveillance procedures are given. Thereafter, medical devices are compared to pharmaceutical products. The specificities of the development of medical devices are presented giving special attention to the users. Finally, conclusions are presented.

2 Definition of ‘medical device’

The Global Harmonization Task Force (GHTF) was formed in 1992 with the goal to achieve greater uniformity between national medical device regulatory systems, but so far a consensus is yet to be reached [101]. Currently, various definitions for the expression ‘medical device’ coexist. In the USA, it appears in section 201(h) of the Food Drug & Cosmetic Act, while in Europe, it is given by the Medical Devices Directive 93/42/EEC. Smaller countries, such as Japan, adopted definitions similar to the one under GHTF guidance. Overall, ‘medical device’ refers to any apparatus, software, material or other similar or related item intended to be used in the diagnosis, prevention, monitoring, treatment or alleviation of a disease or an injury.

The three definitions presented in Table 1 have in common the fact of covering a wide range of products, from simple scales or latex gloves to sophisticated implants or lab-on-a-chip technology. Although the differences between them appear to be subtle they impact the device’s lifecycle with repercussions to manufacturers. For example, as in the USA’s definition the word software is omitted, often producers and distributors are unaware that the Food and Drug Administration (FDA) also regulates these products making them subject to significant civil and criminal liability for noncompliance [102].

According to the GHTF and the European definitions, manufacturers define the device’s intended use. This means that raw materials are not considered medical devices and legislation is only valid when the devices are supplied to the public. Furthermore, the principal intended action declared by the manufacturer defines the rubric under which the device will be included defining the legislation to be complied with.

The phrasing regarding the medical device’s ‘primary intended action/purpose’ is currently responsible for the increasing number of products that are in the borderline between devices and
drugs. Some examples are implantable infusion pumps, drug-eluting stents and single-use syringes pre-filled with medicine.

<table>
<thead>
<tr>
<th>System</th>
<th>Definition</th>
</tr>
</thead>
</table>
| **EU**<sup>1</sup> | any instrument, appliance, apparatus, material or other article, whether used alone or in combination, including the software 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, 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 |
| **USA**<sup>2</sup> | 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 Pharmacopoeia<sup>4</sup>, 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 that does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and that is not dependent upon being metabolized for the achievement of any of its primary intended purposes. |
| **GHTF**<sup>3</sup> | any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent, software, material or other similar or related article:  
a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:  
- diagnosis, prevention, monitoring, treatment or alleviation of disease,  
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,  
- investigation, replacement, modification, or support of the anatomy or of a physiological process,  
- supporting or sustaining life,  
- control of conception,  
- disinfection of medical devices,  
- providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body;  
and  
b) which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means. |

<sup>1</sup> In Medical Devices Directive 93/42/EEC;  
<sup>2</sup> In section 201(h) of the Food Drug & Cosmetic Act;  
<sup>3</sup> In proposed document SG1(PD)/N071R04 - Definition of the Term "Medical Device" posted in March 28, 2011;  

In the USA, medical devices are intended to be used ‘in man or other animals’, which means that veterinary devices are considered medical devices; even though they are under a different jurisdiction from the devices for human use.

Leeches are a bizarre example of the multiple interpretations of the expression ‘medical device’. *Hirudo medicinalis* (medicinal leeches) are blood-sucking aquatic animals that live in fresh water and have been used for clinical bloodletting for thousands of years. Since 2004, FDA has considered them a medical device for mechanical suction of blood, even though they have not
been given a regulatory class [103]. In Europe, they are either considered an animal (e.g. Portugal and France) or a drug (e.g. Germany); they are considered a drug because the ‘principal intended action’ is the release of the drug during the blood suction.

3 Regulatory framework

The first regulatory system for medical devices was created by the United States in 1976 with the Medical Device Amendments. However, it was almost 40 years earlier, in 1938, that the first steps to regulate the commercialization of products used in clinical settings were given with the Food, Drug & Cosmetic (FD&C) Act. According to this document, post-market regulation of medical devices was sufficient to protect public health; its main goal was to distinguish ‘quack’ devices with no medical benefit from the ones that provided legitimate diagnostic or therapeutic benefits. Currently, most of the regulations can be found in Title 21 Code of Federal Regulations Part 800 to Part 1299 (abbreviated to 21 CFR 800 to 1299) and are enforced by the FDA.

In Europe, the first regulatory system dates back to 1993. Prior to that date, each country had its own legislation and the device’s registration varied from country to country [102]. Nowadays, medical devices are regulated by three main Directives: the European Council Directive 93/42/EEC covers most of the medical devices and is supplemented by the European Council Directives 90/385/EEC on active implantable medical devices and 98/79/EC on in vitro diagnostic medical devices. These directives were transposed to each member state’s legislation resulting in a vast legislative framework. To ensure the uniform application of the directives legally non-binding documents were created, such as guidance documents MEDDEV, consensus statements and interpretative documents.

In Europe, the responsibility for the regulatory cycle was assigned to three organizations: competent authorities (Table 2), manufacturers and third party certification organizations – notified bodies (NB) [4].

A competent authority (CA) is a body with the authority to act on behalf of the government to ensure that the requirements of the Medical Device Directives are transposed into each member state National Law and are applied. The jurisdiction of each CA is limited to the country in which was created, but they exchange information and attempt to reach common positions. In addition to the transposition of the medical device directives into National Law, CAs are responsible for appointing and supervising NB, observe medical devices in sale and evaluate adverse incidents. They are also responsible for the approval of clinical investigations and the registration of class I devices and in vitro diagnostic medical device (IVDs) on sale.

Notified bodies are organizations accredited by a member state to assess whether a product meets specific standards. They are independent entities in the sense that they charge fees for their services and do not have any association with manufacturers, suppliers, or installers. They are also impartial and competent, that is, they have qualified staff with special training and all necessary evaluation and verification experience, confidential handling of manufacturers’ files, the application of appropriate methods and testing equipment, the ability to draw up certificates, records, and reports to demonstrate that the controls have been carried out, and carrying liability insurance [4].

The New Approach Notified and Designated Organizations (NANDO) web site [104] has lists of NB. These lists are subject to regular update and include the identification number of each NB as
well as the tasks for which it has been notified. Although the evaluation process should be the same in every NB, currently, there are some variations regarding how they are implemented. In addition, the fees charged vary from NB to NB being determined by the market. However, in the future, this may change since there is a working group in Brussels working in the standardization of both procedures and fees [105].

Table 2: Competent authorities (CA) in Europe for medical devices.

<table>
<thead>
<tr>
<th>Country</th>
<th>Official language</th>
<th>Agency</th>
<th>Webpage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>German</td>
<td>Federal Ministry of Health</td>
<td><a href="http://www.bmgfj.gv.at">www.bmgfj.gv.at</a></td>
</tr>
<tr>
<td>Belgium</td>
<td>Dutch, French, German</td>
<td>CBPH – Federal Agency for Medicines and Health Products</td>
<td><a href="http://www.fagg-afmps.be">www.fagg-afmps.be</a></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Bulgarian</td>
<td>Bulgarian Drug Agency - Department Medical Devices</td>
<td><a href="http://www.bda.bg">www.bda.bg</a></td>
</tr>
<tr>
<td>Cyprus</td>
<td>Greek, Turkish</td>
<td>Cyprus Medical Devices Competent Authority</td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Czech</td>
<td>Ministry of Health</td>
<td><a href="http://www.mzcr.cz">www.mzcr.cz</a></td>
</tr>
<tr>
<td>Denmark</td>
<td>Dutch</td>
<td>Danish Medicines Agency, Inspection &amp; Medical Devices</td>
<td><a href="http://www.medicinskudstyr.dk">www.medicinskudstyr.dk</a>, <a href="http://www.medicaldevices.dk">www.medicaldevices.dk</a></td>
</tr>
<tr>
<td>Estonia</td>
<td>Estonian</td>
<td>Health Board Medical Devices Department</td>
<td><a href="http://www.terviseamet.ee">www.terviseamet.ee</a></td>
</tr>
<tr>
<td>Finland</td>
<td>Finnish</td>
<td>Valvira – National Supervisory Authority for Welfare and Health</td>
<td><a href="http://www.valvira.fi">www.valvira.fi</a></td>
</tr>
<tr>
<td>France</td>
<td>French</td>
<td>AFSSAPS – Agence Francaise de Sécurité Sanitaire des Produits de Santé</td>
<td><a href="http://www.afssaps.fr">www.afssaps.fr</a></td>
</tr>
<tr>
<td>Germany</td>
<td>German</td>
<td>DIMDI – Deutsches Institut für Medizinische Dokumentation und Information</td>
<td><a href="http://www.dimdi.de">www.dimdi.de</a></td>
</tr>
<tr>
<td>Greece</td>
<td>Greek</td>
<td>EOΦ – National Organization for Medicines</td>
<td><a href="http://www.eof.gr">www.eof.gr</a></td>
</tr>
<tr>
<td>Hungary</td>
<td>Hungarian</td>
<td>EEKH – Department for Medical Devices of the Office of Health Authorization and Administrative Procedures</td>
<td><a href="http://www.eekh.hu">www.eekh.hu</a></td>
</tr>
<tr>
<td>Ireland</td>
<td>Irish</td>
<td>Irish Medicines Board</td>
<td><a href="http://www.imb.ie">www.imb.ie</a></td>
</tr>
<tr>
<td>Italy</td>
<td>Italian</td>
<td>Ministry of Labour, Health and Social Affairs - Department of Innovation Directorate General of Medicine and Medical Devices</td>
<td><a href="http://www.salute.gov.it/dispositivi/dispmed.jsp">www.salute.gov.it/dispositivi/dispmed.jsp</a></td>
</tr>
<tr>
<td>Latvia</td>
<td>Latvian</td>
<td>State Agency of Medicines</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>Lithuanian</td>
<td>The State Health Care Accreditation Agency under the Ministry of Health of Lithuania</td>
<td><a href="http://www.vaspvt.gov.lt">www.vaspvt.gov.lt</a></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Luxembourgish, French, German</td>
<td>Ministère de la Santé</td>
<td><a href="http://www.etat.lu/MS">www.etat.lu/MS</a></td>
</tr>
<tr>
<td>Malta</td>
<td>Maltese, English</td>
<td>Malta Competition and Consumer Affairs Authority</td>
<td><a href="http://www.msa.org.mt">www.msa.org.mt</a></td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dutch</td>
<td>Dutch Healthcare Inspectorate</td>
<td><a href="http://www.igz.nl">www.igz.nl</a></td>
</tr>
<tr>
<td>Poland</td>
<td>Polish</td>
<td>Office for Registration of Medicinal Products, Medical Devices and Biocidal Products</td>
<td><a href="http://www.urpl.gov.pl">www.urpl.gov.pl</a></td>
</tr>
<tr>
<td>Portugal</td>
<td>Portuguese</td>
<td>Infarmed – National Institute of Pharmacy and Medicines</td>
<td><a href="http://www.infarmed.pt">www.infarmed.pt</a></td>
</tr>
<tr>
<td>Romania</td>
<td>Romanian</td>
<td>Ministry of Health</td>
<td><a href="http://www.ms.ro">www.ms.ro</a></td>
</tr>
<tr>
<td>Slovakia</td>
<td>Slovak</td>
<td>State Institute for Drug Control, Medical Devices Section</td>
<td><a href="http://www.sukl.sk">www.sukl.sk</a></td>
</tr>
<tr>
<td>Slovenia</td>
<td>Slovène</td>
<td>Agency for Medicinal Products and Medical Devices of the Republic of Slovenia</td>
<td><a href="http://www.jazmp.si">www.jazmp.si</a></td>
</tr>
<tr>
<td>Spain</td>
<td>Spanish</td>
<td>Agencia Española de Medicamentos y Productos Sanitarios</td>
<td><a href="http://www.aemps.gob.es">www.aemps.gob.es</a></td>
</tr>
<tr>
<td>Sweden</td>
<td>Swedish</td>
<td>Medical Products Agency’ ‘Läkemedelsverket’ Medical Devices</td>
<td><a href="http://www.lakemedelsverket.se">www.lakemedelsverket.se</a></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>English</td>
<td>MHRA – Medicines &amp; Healthcare products Regulatory Agency</td>
<td><a href="http://www.mhra.gov.uk">www.mhra.gov.uk</a></td>
</tr>
</tbody>
</table>
The medical devices regulations not only confirm the device's safety and/or effectiveness but also guarantee that they meet quality standards [2]. In general, these standards are created by entities such as the International Organization for Standardization (ISO) or the Association for the Advancement of Medical Instrumentation (AAMI) and must be complied by those who make the products (manufacturers), who sell them (vendors) and also by those that use them (users). The quality systems for FDA-regulated products are known as Current Good Manufacturing Practices (CGMPs). Due to the diversity of products (food, drugs, biologics, and devices), the regulations provide a framework that all manufacturers must follow and adapt to their reality. Medical devices must abide the Quality System Regulations (QSR) - QSR CFR Part 820 - which is based on ISO 9001 and ISO 13485. In Europe, the quality management systems are described in the Annexes II and V of the Medical Device Directives. These annexes do not stipulate the type of quality system but is generally agreed that Annex II is equivalent to ISO 9001 plus ISO 13485 and Annex V is equivalent to ISO 9001 plus ISO 13485 without any design control.

The components of a typical regulatory framework are summarized in Figure 1.

![Figure 1: Components of a typical regulatory framework (adapted from [3]).](image)

## 4 Classification

Medical devices can be classified according to several criteria. From an academic point of view and considering the stage of healthcare in which they are used, they can be categorized as preventive (e.g. dental floss), diagnostic (e.g. x-ray), therapeutic (e.g. nasogastric tube) and assistive (e.g. splints). It is also possible to distinguish between medical devices for general use (e.g. stethoscope) and disease-specific (e.g. implants) [2].

Considering the number of utilizations, there are devices for single use (e.g. needles) and multiple use (e.g. blood pressure meter). This means that there is a distinction between ‘placing a device on the market’, i.e., start its commercialization, and ‘putting a device into service’, that is, start its use after installation. This distinction raises health and clinical safety issues pertinent in clinical practice, namely the performance and effectiveness and the exposition of both patients and staff to unnecessary risk [4].
The nomenclature created by the Global Medical Devices Nomenclature (GMDN) Agency was created to meet the need to implement legislation; regulators in the European Economic Area (EEA), request the use of GMDN to support the conformity assessment process required for CE marking. GMDN consists in a system of expressions, which divides the entire medical device product market into 20 possible categories (of which 16 are presently established) based on the device’s application, technology, or other common characteristics, to name and describe medical devices, used to name and describe medical devices [5], [106].

Table 3 summarizes the medical device’s classification in Europe, the USA and according to GHTF, as far as risk to both patients and users is concerned. In spite of the classes being similar, products considered class II or III in the USA might carry a different classification in Europe. The risk categorization is related with the approval process: the higher the class, the more demanding the process is.

<table>
<thead>
<tr>
<th>System</th>
<th>Class</th>
<th>Risk level</th>
<th>Regulatory control</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU*</td>
<td>I</td>
<td>Non-sterile Non-measuring Low</td>
<td>Annex VII + Annex V for Sterile / Measuring aspects</td>
<td>Surgical gauze Wheelchairs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sterile Measuring</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIa</td>
<td>Medium</td>
<td>Annex II or Annex VII + V or Annex VII + VI</td>
<td>Hearing aids Ultrasound equipment</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>High</td>
<td>Annex II or Annex III + V or Annex III + VI</td>
<td>Infusion pumps Surgical lasers</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>High</td>
<td>Annex II or Annex III + V</td>
<td>Prosthetic joints Stent-grafts</td>
</tr>
<tr>
<td>USA</td>
<td>I</td>
<td>Low</td>
<td>General controls</td>
<td>Adhesive bandages Hospital beds</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Moderate</td>
<td>General controls Special Controls Premarket Notification [510(k)]</td>
<td>Blood pressure cuffs Sutures</td>
</tr>
<tr>
<td>GHTF</td>
<td>A</td>
<td>Low</td>
<td>Surgical retractors Tongue depressors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Low-moderate</td>
<td>Hypodermic needles Suction equipment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Moderate-high</td>
<td>Lung ventilator Bone fixation plate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>High</td>
<td>Heart valves Implantable defibrillator</td>
<td></td>
</tr>
</tbody>
</table>

* The annexes refer to the council directive 93/42/EEC

Both the GHTF and the European Union (EU) apply a set of rules to determine the device’s class assuring that the same classification is attributed by multiple entities. The European classification requires understanding and interpretation of 18 rules available in Annex IX of the Medical Device Directive. These rules classify devices based on potential hazards and possible failure, duration of contact with the body, degree of invasiveness, and local versus systemic effects. The European
rules correspond, to a large extent, to the classification rules established by the GHTF in the guidance document GHTF/SG1/N15:2006.

The Food and Drug Administration has established classifications for approximately 1,700 different generic types of devices and grouped them into 19 medical specialties – panels. Each device was then assigned to a regulatory class based on the level of control necessary to assure the safety and effectiveness of the device. This classification is risk based and depends both on the intended use and indications for use of the device. In order to determine a device’s class, as well as whether any exemptions may exist, one has to look for the device’s name, or part it, in the online FDA’s Product Classification Database [107]. Since May 2011, Europe has a similar databank – European Databank on Medical Devices (EUDAMED) – but, for now, is not publicly accessible [108].

Currently, the disparities of medical devices’ classification systems between countries pose considerable difficulties limiting their implementation globally [102].

5 Pathway to market

As far as medical devices are concerned, the differences between Europe and the USA are not limited to the risk classification system. The path manufacturers must follow to launch their devices is also noticeably different. While in the USA, FDA ensures that medical devices are ‘reasonably’ safe and effective, in Europe, manufacturers must only demonstrate that the device is safe and performs according to its intended use. This subtle dissimilarity is responsible for significant differences in the speed of introduction of the devices into the market and the amount of tests the devices must pass. It is also responsible for the fact of innovation being considered faster in Europe. Both procedures are described in the following sections.

5.1 Europe

As far as medical devices are concerned, when referring to Europe or the European Union, one is referring to the current member states plus the candidate countries and the members of the European Free Trade Association (Norway, Switzerland, Iceland and Liechtenstein).

A medical device to be commercialized in EU has to present a CE mark (abbreviation of French "Conformité Européenne" meaning "European Conformity"), Figure 2. This mark is not a guarantee of safety, simply states that the manufacturer claims that the relevant Essential Requirements in the Directives are complied and the device is fit for its intended purpose. In addition, it signifies that the product can be freely marketed anywhere in EU without further control.

![CE mark example](image)

Figure 2: Example of the CE mark with the number of the notified body (xxxx).

The Essential Requirements in the Medical Device Directive 93/42/EEC can be divided in two groups: the first refers to a set of general requirements for safety and performance that applies to all devices, while the second is a list of specific and technical requirements regarding design and manufacturing that may or may not apply depending on the nature of the device.
In order to obtain a CE mark for their devices, manufacturers have to demonstrate and document compliance with the regulations and issue a declaration of conformity. In certain situations, such as class I sterile devices, it may be required the intervention of a Notified Body. Class III devices require clinical studies, except when data already exists. The evaluation process may take between three days to several months depending on the class of the device, the size of the manufacturer, the size of the technical file and the duration of the clinical study. Figure 3 summarizes the process; it should be noticed that manufacturers can choose among methods for ‘conformity assessment’ of the device and/or manufacturing system.

Figure 3: Flowchart with the European path to market.

In the case of devices for clinical investigation and those that are custom made, the CE mark is not mandatory. The manufacturer has to follow Annex VIII and declare that their products conform to the Essential Requirements.

Clinical data is intended to demonstrate the device’s safety and that it performs as intended by the manufacturer. In this context, the expression has a broad meaning and includes everything from bench testing to clinical trials in humans. It can be compiled from the literature or result from specifically designed clinical investigations. If the later path is chosen, manufacturers must abide the standard ISO 14155 and the clinical trials must be pre-approved by a Competent Authority.

Currently, the EU has 27 member states and 23 official and working languages. This affects the regulatory regime in two ways. First, labels and instructions must be translated into the national language of the country where the device is used. Second, manufacturers must provide evidence
that the documents are translated when they are submitted to the Competent Authority before placing a product on the market [4].

5.2 USA

Medical devices for human use are regulated by the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation & Research (CBER) of the FDA [109]. Although this governmental agency allows third parties - accredited persons - to conduct the primary review of some devices, it retains final authority over all devices’ approval. In order to market a medical device, there are four options: ‘exempt’, 510(k), premarket approval (PMA) and the humanitarian device exemption (HDE).

Most class I and some class II devices are exempt from the premarket notification 510(k) requirements. Nonetheless, they still have to comply with the general controls, that is, they must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have establishment registration and device listing forms on file with the FDA.

The 510(k) process is a 90-day review procedure based on the argument that the device to be marketed is at least as safe and effective, that is, substantially equivalent (SE) - predicate device - to one that was already approved by the FDA and is not subject to PMA. Most class II devices follow this path. In addition to the premarket notification 510(k) and the general controls, devices must comply with special controls, namely performance standards, guidance documents or implementation of post-market surveillance.

PMA can be compared to the design dossier that is needed to market European class III devices. It is the most stringent type of device marketing application; it is the process to evaluate the safety and effectiveness of class III medical devices. Although, FDA regulations provide 180 days to review the PMA and make a determination, the process can take between 6 months to 2 years, depending on factors such as the report of clinical studies, quality of documents and the amount of time necessary for the manufacturers to response to FDA concerns.

Prior to the FDA Modernization Act of 1997 (FDAMA), if an innovative device was found not substantially equivalent (NSE), it was classified as class III and a PMA was required resulting in a conflict between the need of being innovative and a more complex commercialization process. Currently, the de novo process allows the reclassification of the devices to class I or class II providing a simpler route to market for novel low risk devices. This process, which has to start within 30 days of an NSE letter, has a review period of 60 days and, if the device is classified into class I or II, the applicant receives an approval order to market the device. However, if it is determined that the device must remain in the class III category, it cannot be marketed until the applicant has obtained an approved PMA.

The use of the de novo route is a strategic decision and depends upon the product. The adoption of such route is influenced by factors such as the device’s market and other barriers to market entry. For example, if there is insignificant patent protection, manufacturers can benefit from a class III classification because it will represent to competitors a barrier to market entrance.

The Humanitarian Device Exemption (HDE) is a specific path for class III medical devices designed to address diseases and conditions that affect fewer than 4000 patients in the United
States per year. This path aims to be an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting small populations.

Figure 4 summarizes the process to market a device in the USA.

![Flowchart with the USA path to market](image)

Figure 4: Flowchart with the USA path to market; SE – substantially equivalent; NSE – not substantially equivalent.

6 Market

Several sources describe the medical device industry as dynamic and in continuous growth. Eucomed, an European association of the medical technology industry, claims that, in Europe, there are almost 22 500 medical technology companies (80% are small and medium enterprises) employing nearly 500 000 people and generating €95 billion [110]. The USA’s market is considered the world’s largest and is estimated to worth US$105.8 billion in 2011 [111].

The growth of the sector can be explained by a series of factors, such as the aging of the population and the consequent increase of diseases and co-morbidities, the demand for healthcare technologies and services, and the evolution of the character of illnesses from acute and infectious types towards chronic ones. In addition, citizens have increasing expectations regarding their health and the services and products they receive. The increased focus on prevention, e-healthcare and the shift to community care and homecare led to the development
of new market segments. Despite the variety and quantity of existing medical devices, the sector will continue to grow also due to limited availability of healthcare solutions in low-income countries and the lack of information on the types of devices needed.

A restriction to the growth of the sector is the fact of medical technology being considered a cost-driving force; this puts the medical device industry under intense scrutiny and regulation, and healthcare payers and purchasers, namely governments and insurance companies, demand the demonstration of the products cost/benefit. This analysis creates expectations regarding the quality of the medical care and the efficacy of the treatment. Furthermore, the results decide if coverage is provided impacting directly on the manufacturers’ attainable revenues.

The demand for medical devices is driven, in one hand, by the ‘demand pull’ of the aging population and, on the other, by the ‘technology push’ of new medical technologies due to both patients and doctors seeking the latest technologies for treatment.

The industry is highly fragmented and consists of small niche markets with few products. Most companies are small and medium-sized and it is common to start as a university spin-off relying in a single device or technology. For this reason, often companies have limited resources to face the regulatory requirements and it is difficult for them to survive a failure in the marketplace. Mergers and strategic alliances are frequent, representing quick and effective ways of manufacturers to gain new product lines and technologies as well as enter new markets.

The development of medical devices is both capital and technologically intensive. New technologies are generally brought to market by start-up companies while large companies develop successive iterations of existing devices. As medical devices are highly substitutable by similar products with superior efficacy, profits depend on new solutions which compel manufacturers to be constantly innovating, researching and presenting new solutions.

7 Post-market surveillance

In the case of medical devices, as they involve human safety, manufacturers have two obligations when they deliver a device to market: post-market surveillance and adverse event reporting [6]. The first consists of active monitoring of medical devices during their use and allows the detection of rare but serious adverse events and long-term failures that are unable to be detected during the pre-market surveillance due to the short duration of the clinical studies and/or the limited number of participants. In addition, it allows the identification of complications related to inexperience and improper use of a device. It also helps to identify ‘off-label use’ of the devices and problems related with the manufacturing process. The risk that was estimated before the device entering the market can now be actually measured and the data gathered is essential to monitor the device’s safety and effectiveness that is used to determine if the device merits coverage from governments and/or reimbursement agencies. The data is also used for the development of new versions of the devices or completely new products.

An adverse event refers to those situations that led (or might have led) to one of the following outcomes: serious injury of a patient, user or other person, death of a patient, user or other person, severe deterioration in state of health of a patient, user or other person or significant damage to the medical device. Regulators must be informed of these events and the reports may arrive from three sources: manufacturers who report a serious injury or a death; users and other third parties who report the malfunction of a medical device; and competitors who complain
about noncompliance by another manufacturer. FDA maintains a database, called Manufacturer and User Facility Device Experience Database (MAUDE), to collect such data [112].

The adverse event reporting is a passive process since reports are received as they occur and are reported; it can be said that is unreliable and allows a large proportion of events underreported. Furthermore, it does not provide data regarding the number of devices at risk for a given adverse event making impossible to calculate an incidence rate.

Especially in the United States, adverse events can lead to legal disputes with manufacturers, health care providers and/or operator that are responsible for the reduction of income due to liability charges as well as reduction of sales by harming the customer's confidence in the manufacturer.

One of the goals of post-market surveillance is to reduce the likelihood of a same type of adverse incident being repeated in a different place at different time. Thus, both manufacturers and healthcare systems are held responsible for the proper functioning of medical devices.

8 Medical devices vs Drugs

Like drugs, medical devices contribute to better quality of life and are essential for effective prevention, diagnosis, treatment of illnesses and diseases. Both have become integral part of modern healthcare and have intellectual property issues. The major difference between them lies in the definition: unlike medical devices, drugs achieve their principal intended action in or on human body by pharmacological, immunological or metabolic means. Drugs interact with a patient directly while most medical devices typically interact with patients through an intermediary - the healthcare professional. Furthermore, devices produce mainly local and physical effects on the body rather than systemic and pharmacological [4].

Medical devices vary in size, durability (from disposable to implantable), complexity, packaging and use. Their performance depends on the device itself and how it is used. Many devices require service and maintenance while many others are dependent on infrastructure, therefore, being difficult to use in low-income settings.

Medical devices are associated to improvements of quality of life and time-saving. However, adequate and/or device-specific training are required with the learning curves of these products being longer.

Figure 5 shows typical product life cycle curves for medical devices and pharmaceutical drugs. While the development of a medical device generally is short [7], the development of a new drug takes around a decade to conclude. However, once its safety and efficacy is determined, it remains unaltered for decades. On the other hand, medical devices have faster cycle times and are characterized by incremental improvements, that is, the information (on performance, safety and efficacy) gathered by the first versions is used to upgrade the following generations. This can be explained by the constant interaction between users and designers.

Regarding clinical trials, the methods used to access the quality, safety, and efficacy of pharmaceuticals is inadequate for testing medical devices; it is difficult to have placebo controls for most devices or double-blind patients and physicians regarding who is getting which technology. In addition, the size of target populations for many devices makes impractical to conduct randomized clinical trials (RCT) [7].
Payers have different expectations from drugs and devices: they demand a higher level of efficiency of drugs while with medical devices they care about effectiveness.

As far as supply is concerned, both drugs and medical devices need a supply chain. However, there is no well-defined supply chain or profession, such as pharmaceuticals, involved in the supply of medical devices.

Comparing both industries, the pharmaceutical industry is considered a powerful force while the medical device sector is recent and composed by smaller companies. Drugs have been subject to internationally agreement upon methods and research protocols for decades; regarding medical devices a consensus is yet to be reached.

![Figure 5: Typical product life cycle curve for medical devices and drugs.](image)

9 Medical device users

During product development, it is commonly accepted that the involvement of customers contributes to successful products, i.e., products that accomplish a desired aim, are known by the target audience and lead to growth and shareholder value. In fact, several tools, such as quality function deployment (QFD) [8] and the Kano model [9], have been developed to identify customers’ needs and demands and translate them to design targets. In the healthcare sector, users play an equally important role [10] and those tools are also applied [11-13]. However, special attention must be given to the fact that, in this sector, there are multiple users who, besides having distinctive perspectives of the devices, use them differently and with dissimilar expectations. Furthermore, since devices are frequently bought on behalf of the end-user and the end-user is not directly responsible for the payment of the device or treatment, it is important to define the terms ‘customer’ and ‘user’.

Customer can be defined as a person or company who purchases goods or services independently of benefiting from them. In their work, Shah et al. [14] presented a definition and a classification of medical device users, Figure 6. The authors distinguish ‘medical device user’ from ‘medical device end-user’. The first refers to ‘a person who uses a medical device for the treatment and/or care of him-/her-self or someone else’, while the latter refers to ‘a person who
is the ultimate beneficiary of the usage of a medical device and who can also be the user of a
medical device if using the medical device for him-/her-self’.

In order to involve both users and customers in the development of novel devices it is
necessary to engage and communicate with them. Although this self-evident point appears to be a
trivial task, it may reveal itself extremely complicated due to numerous barriers, such the diversity
of stakeholders or ethical and research governance procedures. Other aspects that must be
considered are the users’ availability, training and technological knowledge.

During the identification of the users, it is important to understand the context in which the
devices will be used, the cultural and anatomical differences as well as behavioral changes that
may occur.

The fact of the user not being the payer not only affects the customer-manufacturer relation
but also impacts the device’s adoption. Regarding the first, the manufacturer may face difficulties
identifying the users’ needs and the environment in which a device will be used and, in addition,
cannot estimate the device’s value and the customers’ willingness to pay. Regarding the device’s
adoption, questions about conflict of interest may be raised; sales representatives are essential in
training physicians to use devices but they must provide information free of bias and financial
inducements. One should also have in mind that the human nature makes people’s perspectives
change depending on whether they are dealing with abstract statistical populations or with their
family [7].
Product development refers to the process of creating products with new or different characteristics to offer fresh or additional features to the customer. Normally, it is triggered by a need or an idea. Then, the design team identifies the specific problems that customers intend to solve purchasing a good or service (customer needs) and generate concepts. From the panoply of concepts, only one is developed and optimized. Following this, prototypes and/or small series are produced. These pre-series are evaluated by a restrict number of clients or by certifier companies. The process ends with the launch of the product in the market. While some authors describe this process with only 5 steps, others name as many as 25 stages [15].

In the case of medical devices, the development of new products is incremental with each model slightly different from the previous generation [4]. Furthermore, it is both capital and technologically intensive requiring highly qualified personal with different backgrounds ranging from medical doctors to engineers.

It is often the case that design requirements are incomplete, complex and result from ambiguous situations. Thus, in order to have a complying product, the cost and complexity of the device can be high. An example is the treatment of aortic aneurysms; currently there is little information about what happens inside the aneurysm sac after the introduction of stent-grafts.

The healthcare sector is dynamic with research happening in every direction. During the development and introduction in the market of a novel device, this must be considered because it can lead to a new competitive product jeopardizing the success of the device being developed. One should also consider the innumerous stakeholders, especially healthcare policy makers, because they affect the device’s adoption and, consequently, the manufacturer’s revenues.

Regarding the development process of medical devices, the few publications that exist are mostly focused on one topic. For example, the standard ISO 14971 specifies processes for the identification of hazards associated with medical devices; the standard IEC 62304 specifies life cycle requirements for the development of medical software and software within medical devices; and, the Quality System Regulation (QSR) from FDA establishes quality systems. Thus far, to the authors’ knowledge, there is not a document that explains how to address the multiple peculiarities of medical devices. Such document could help designers to tackle the complexities of the environment that surrounds medical devices. Furthermore, medical device designers could benefit from a methodology that showed which standards and regulations should be addressed at each moment in time.

Conclusion

In spite of medical devices having several particularities that cannot be neglected, namely multiple definitions, classifications and stakeholders, they can be compared to other sectors. For example, with the aerospace sector; in both cases, human safety is involved, there are many standards and regulations to be considered and sophisticated technological and engineering solutions are used.

Considering the characteristics presented here, the medical device industry would benefit from a dedicated product development methodology to guide the development process. The use of such methodologies would contribute to costs savings and the launch of new products more quickly, effectively and efficiently.
A product development standard represents a mechanism for communicating: the team knows what and how has to be done. It also avoids waste, supports decisions and allows reviewing the process’ output. As far as medical devices are concerned, a structured product development methodology is expected to increase the devices acceptance, improve the device’s safety and efficiency and reduce device recalls. It would also represent a more effective risk management and quality assurance. Furthermore, it would reduce delays that result in low product sales and profitability, and loss of potential market share. Overall, and considering the type of companies in the sector, the use of dedicated product development methodologies could contribute to improve the company’s image and assist to obtain funds for further researches.

The use of a dedicated product development methodology may help designers capture correctly the customers’ needs and conceive the ideal device. At this point, the success of the new product will depend on the ability of the manufacturer to materialize its design. In this paper, the peculiarities of medical devices that impact the design phase were addressed; however, in the future, it is important to understand which characteristics are unique to the manufacture of medical devices and how they can be successfully addressed.

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