UNIVERSITA' POLITECNICA DELLE MARCHE

FACULTY OF ENGINEERING

Master degree in Biomedical Engineering

MEDICAL DEVICE REGULATION IN THE EUROPEAN COMMUNITY:

EU MEDICAL DEVICE REGULATION (MDR) vs. MEDICAL DEVICE DIRECTIVE (93/42/EEC) AND ACTIVE IMPLANTABLE MEDICAL DEVICE DIRECTIVE (90/385/EEC)

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Contents

INTRODUCTION

The world of medical devices in this last year, 2020-2021, is facing with two major challenges: Covid-19 global pandemic, which requires more devices than usual and the entry in force, postponed in May 2021, of the new European medical devices Regulation 2017/745 (MDR) repealing the actual Medical Device Directive (MDD) 93/42/EEC and the Active Implantable Medical Device Directive (AIMDD) 90/385/EEC.

From 1993 until now, the medical device field is ruled by the actual 93/42/EEC MDD that, over time, has some lacks in the traceability process of medical devices, low clinical evaluation, unclear roles of economic operators and scandals refer to breast implants.

In 2017 the European Commission decided to issue a new medical device Regulation known as a revolution in the medical device area.

The new MDR redefines not only the entire structure based on the number of the articles and chapters but also introduces and clarifies new figures and more clear roles of people that is involved.

The new measures introduced by MDR will came into force in May 2021, after a year postponing, and will disrupt the industries of medical devices that want to commercialize a medical device in Europe.

For this reason, that there is the need to understand and to study the new features of the MDR respect to the actual and still valid MDD in order to place in the right way the devices on the European market.

This thesis has the aim to point out and describe the main features of the Directives (93/42/EEC and 90/385/EEC) and the new Regulation, analyzing the changes and challenges for the future.

The entire work is organized in four Chapters after a detailed literature review based on scientific articles and on the two Directives and Regulation uploaded on the official European Commission website.

In detail, the first Chapter introduces the world of medical devices starting from the definition of a medical device and analyses the global market to the procedures to be place on the market a device and relative classification.
Chapters three and four outline the main features of the actual Directives (MDD and AIMDD) and describe the new MDR with a small focus on the application of the MDR to the Covid-19 medical devices.
In the last Chapter a comparison between Directives and Regulation has been made in order to understand the novelties and the future challenges that companies face, applying the new guidelines of the Regulation.

Chapter 1

MEDICAL DEVICES

The aim of this section is to present the wide world that characterizes medical devices. Starting from the definitions and clarification of the meaning of the term "medical device", according to the European directives, then, moving on the analysis of the global market and eventually arriving to the mandatory procedures for the marketing and their classification based on different criteria.

1.1 Definition and scope of a medical device

The term medical device has been in existence for centuries from the Egyptians until now [1,2]. There is evidence that scalpels, slings, splints, crutches and other medical devices were used as far back as 7000 BCE by the Egyptians [1,2]. In 1950, thanks to the first artificial hip replacement and the first commercially available artificial heart valve, that began to realize the idea of a medical devices. In 1993 was developed the first European union regulatory system for medical devices [2].

From 2000 till the present days, we are witnessing a great development of assistive robotics as a help in people showing functional disabilities. This new branch of engineering, integrated with information systems or web-based system, is becoming a reality of the medical device world with its pros e cons [2].

Nowadays defining what is and what is not a medical device is not that easy. This difficulty lies in different reasons, one of which is given by the multiplicity and diversity of devices [2].

The term medical device indicates, in fact, a category of products, characterized by strong heterogeneity (Figure 1, Right). For this reason, it is important to uniquely define the concept of medical device.

Diverse regulatory organizations have formulated a variety of definitions for a medical device, but, currently the ultimate definition is dictated by the Medical Device Directive (MDD) that defines a medical device as:

"Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including 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, treatment, alleviation 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 the pharmacological, immunological or metabolic means, but which may be assisted in its function by such means [4].

From the previous definition, it is possible to notice that talking about medical device implies a series of tools, useful to humans, in order to take care of their health.

Once defined the specific definition for a general medical device they can be classified on the basis on their purpose.

In this thesis, the attention is paid both on medical devices (93/42/EEC) and on active implantable devices (90/385/EEC), since the directives, addressed in the following chapters, involve both of them (Figure 1, Left).

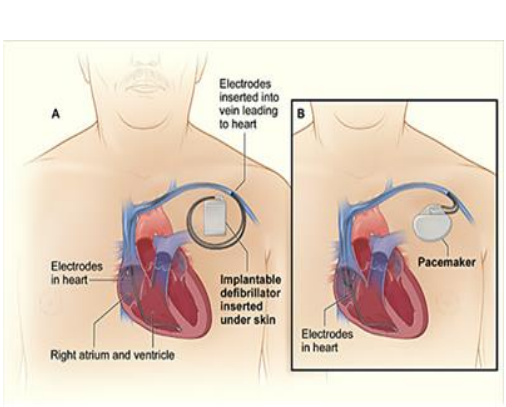
In order to understand the meaning and the applications of implantable and active medical device both the definitions have been analysed separately.

According to the MDD, an active medical device is [4]:

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

In the same way, the definition of the **implantable** device is:

"Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device".



Implantable Cardioverter Defibrillator and Pacemaker

Figure 1: Right: Different areas of medical devices world; Left: Example of an active implantable device [5].

1.2 Medical devices market

According to the International Trade Administration (ITA), sales of medical device is estimated to increase by 6.4% annually from 2016 to 2020, reaching nearly US $ 440 billion. While the United States is projected to remain the world's largest medical device market, the Asia/Pacific and Western Europe markets are expected to expand at a faster pace over the next several years [7]. This can be confirmed by the growth trends visible in Figure 2.

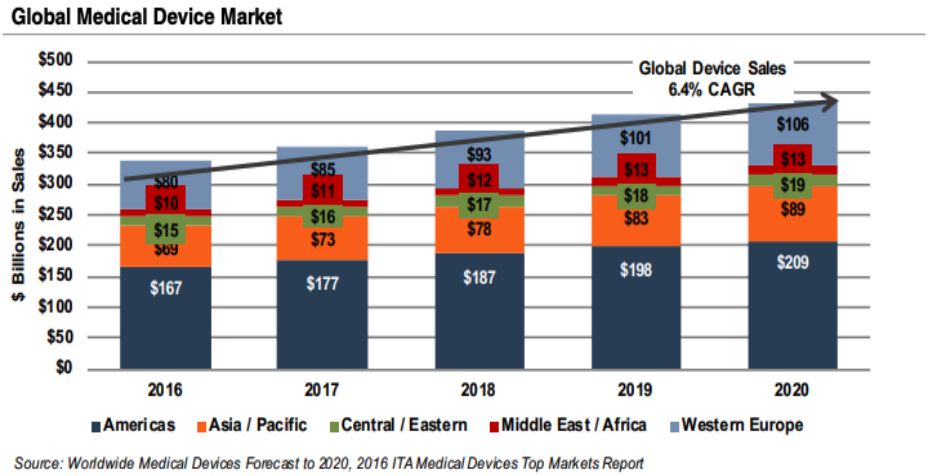


Figure 2: Global Medical Device Market development.

From Figure 2, it is possible to highlight global device sales growth, evaluated with the compound annual growth rate (CAGR), from 2016 to 2020. This rate is estimated to rise at 5.3% for the period of 2017-2022 [8].

The sudden growth of the device market is given not only by continuous technological innovations but above all by the high rate of seniority of the population that increasingly requires greater assistance. According to the United Nations projections, the world's elderly population will increase from approximately 610 million (8.3% of the world population) in 2015 to 1.8 billion (17.8% of the world population) in 2060 [8]. These facts indicate a market growth

potential in the field of innovative medical device solutions in which the 2020 top 30 global medical device companies are located (Annex I of the thesis).

Since this work focuses on what are the regulations regarding medical devices and in particular active implantable devices, it is appropriate to analyse the emerging market of these.

From the previous definition of an active implantable device, it is possible to understand how the category includes different kinds of devices. Examples are cardiac pacemakers, implantable cardioverter defibrillators, nerve stimulators, cochlear implants and ventricular assist devices [9]. Against this broad category, market will be also segmented based on the product, application and end-user, i.e. hospitals and clinics [9].

As describes in Figure 2, North America, Europe and Asia Pacific hold the world record in marketing. Especially, North America is expected to dominate the market in the forecast period due to the rise in the number of people suffering from arythmia and the early launch of technologically advanced products by companies [9]. At the second place it is possible to find Europe for the neurological disorders and for a rapid adoption of the advanced technologies and, following, Asia Pacific with the occurrence of cardiovascular diseases and arrhythmia because of the changing lifestyle and adoption of western culture [9].

Hence, healthy and technology represent the two major reasons which helps rapid growth of the active implantable medical devices market (Figure 3) [9].

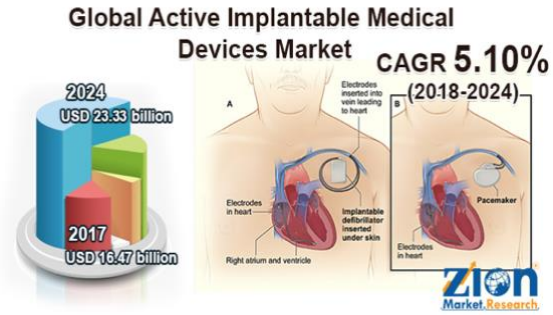


Figure 3: Global Active Implantable Medical Device Market.

Also, in this case, as it was performed for the global medical device market (Figure 2), CAGR rate is evaluated at 5.10% from 2018-2024.

1.3 Marketing placing of the medical devices and CE conformity

Each medical device can only be placed on the market and/or put into service when the product complies with the provisions of all applicable directives and when the conformity assessment has been carried out in accordance with all the directives [3].

A *Directive* is defined as a legislative act that sets a goal that all European countries must achieve. Each State is free to choose how to proceed, in terms of form and means to be used [10].

Above the directives, in the legal field, the European regulations, issued by the European Parliament and Council, must be taken into account.

A *Regulation* is a binding legislative act. It must be applied in all its elements throughout the European Union.

Currently, the European and national regulatory framework on medical devices includes three main directives that regulate the three categories of devices:

-*Active Implantable Medical Device Directive (AIMDD 90/385/EEC).*

-*Medical Device Directive (MDD 93/42/EEC).*

-*In-Vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EEC).*

These have been supplemented since several necessary update, due to the new and emerging technologies which have challenged the current framework, highlighted gaps and pointed to a certain scarcity of expertise [3,11].

The aforementioned directives form part of marketing process of medical devices in the 28 countries of the European Union and the European Economic Area (EEA) [1].

At the base of these directives there is a system defined as “New Legislative Framework”, adopted in 2008, useful to improve the internal market for goods and strengthen the conditions for placing a wide range of products on the EU market (Figure 4) [1,12].

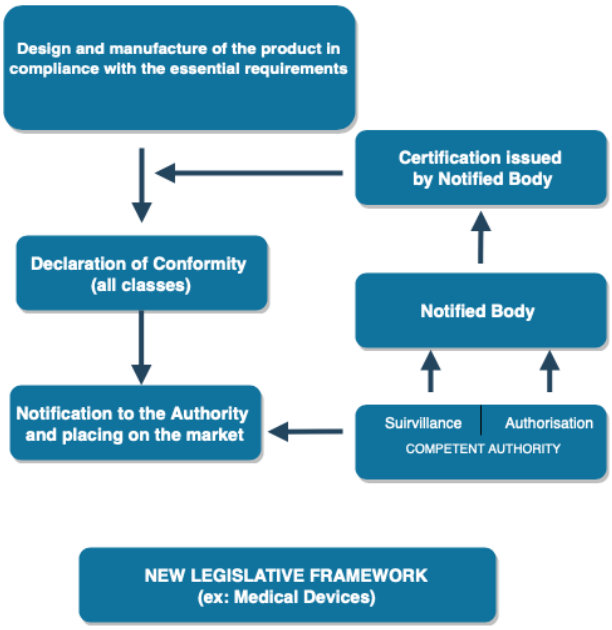


Figure 4: New Legislative Framework system for placing medical device on the market.

Through the New Approach directives, the EU legislator dictated general rules and principles of safety and performance, or the minimum requirements, that regulated products must meet in order to circulate freely in the countries of the European Union.

One of these requirements is the affixation of the CE conformity marking (Figure 5) [3]. This is a conformity mark which all the European medical devices must have before they can be put on the market.

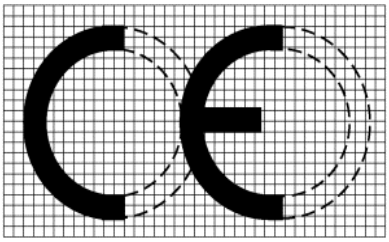


Figure 5: CE conformity mark.

The CE conformity mark, defined by "CE" initials, follows these two technical characteristics. The various components of the CE marking must have substantially the same vertical dimension, which may not be less than 5 mm, although this minimum dimension may be waived for the small-scale devices [3]. The second point regards the choice of the two CE initials. They don't stand for any specific words, but it is a symbol that is seen as a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation [3]. It must appear on many products traded on the extended Single Market in EEA [12].

By affixing the CE marking to a product, a manufacturer declares that the product meets all the legal requirements for CE marking and can be sold throughout the EEA [12]. This mark brings benefits for both categories, companies and consumers. Businesses know that products bearing the CE marking can be traded in the EEA without restrictions, at the same time, consumers enjoy the same level of health, safety and environmental protection throughout the entire EEA [12].

The conformity assessment is referred to in the two directives 93/42/EEC and 90/385/EEC in annex II and in regulation (EU) 2017/745 in annex V, which they will be discuss in the following chapters.

Finally, the directives constitute an integral part of placing a device on the market. Independently from the type of the medical device, they provide systematic procedures for the supervision and control of medical devices. They indicate series of essential safety requirements and other needs of collective interest, such as the effectiveness, which the product must comply with. The compliance of these requirements will be entrusted at the competent authorities, notified bodies, but also the users and manufacturers themselves who are required to prepare a technical dossier that includes documentation relating, for example, to design, risk management, procedures relating to post-marketing surveillance and many other parameters listed in the annexes section of each directive.

1.4 Classification of medical devices

As previously mentioned, the universe of medical devices is diverse with wide variations in potential severity of harm to the patient or user. From that, it should be noted that medical devices, given the extreme heterogeneity of the category, do not all have same clinical impact, nor the same degree of potential risk. For this reason, they are subdivided into four classes of increasing risk with the relative conformity assessment and procedure. The classification step, therefore, is the first act that the manufacturer must perform in order to identify the class of the device, according to the rules contained in Annex IX of D.Lgs 46/97 [13]. The subdivision consists in four product classes; Class I, Class IIa, Class IIb and Class III, based on the vulnerability of the human body and on the potential risks that they could cause to the patient (Figure 6).

Figure 6: Classification of medical devices under MDD.

From Figure 6, it is possible to notice the different groups based on the level of the risk. The risk class of a medical device is determined by four factors as the level of invasiveness, duration, type and function. Going in detail, how long the device is intended to be in continuous use, if it is implantable or active, surgically invasive or not and if it contains substances.

For each class, the manufacturer must comply with conformity assessment procedures, Rules, which vary from class to class. For example, for Class I devices the checks can be carried out in principle by the manufacturer himself, on the contrary, for Class IIa, IIb and III devices, which have a high-risk potential, a control by Notified Bodies is required both in the design phase and in the manufacturing phase of the devices.

This means that the manufacturer must demonstrate that not only his product, but also the production process in its various aspects (design, manufacturing, controls, etc.), comply with the essential requirements.

The classification criteria, which the manufacturer must comply with, are collected in Article 9 and Annex IX of 93/42/EEC directive and in Article 51 of

the new European medical device regulation (MDR) 2017/745, dealt with in the following chapters.

Chapter 2

OVERVIEW OF THE TWO DIRECTIVES: 93/42/EEC AND 90/385/EEC

The aim of this chapter is to retrace the fundamental points of the two European directives present to date in the field of medical devices, starting from their birth up to the problems that led to their repeal.

2.1 93/42/EEC and 90/385/EEC European Directives

As previously defined in chapter 1, the term medical device includes a wide range of very different products: from devices for personal use to implantable devices.

For this reason, that is for the wide range of products present, the European Commission has issued directives in order to guarantee safety and protection to its buyers. These directives are intended to regulate, in the European Union countries, the sector of medical devices in all its aspects, i.e. clinical evaluation, essential requirements, CE conformity, market placing and classification. These points will be addressed and described by the two directives examined in this thesis: 90/385/EEC and 93/42/EEC Directives.

Directive 93/42/EEC Medical Device Directive (MDD) of June 14, 1993, transposed with Legislative Decree 46/97, is currently considered to be the main European directive in the field of medical devices [4]. It consists of 23 articles, including a further article, “Article 9 bis” and 12 Annexes identified with Roman

numerals. Compliance with the revised directive became mandatory on 21 March 2010. It is being repealed and replaced by the 2017/745 European Union Medical Device Regulation (MDR), from 26 May 2020, that will be discussed in the next chapter.

Directive 90/385/EEC of 20 June 1990 and implemented with Legislative Decree 507/92 is addressed exclusively to active implantable medical devices. It is made up of 17 Articles and 9 Annexes which in this case are indicated by natural numbers.

The main points of the 93/42/EEC regulation will be described and analysed to the detriment of the 90/385/EEC directive, as it is addressed to a specific field of devices. Despite this, both directives have annexes of fundamental discussion in the manufacture, safety and sale of medical devices.

2.1.1 Essential Requirements

The essential requirements consist of safety, design and manufacture requirements that a medical device must comply with in order to be placed on the market and to circulate freely in the European Union. This issue is described in Article 3 and Annex I of both directives described above [4,11].

The list of these requirements is divided into two parts: the first section is dedicated to the general requirements and the second section to the requirements regarding design and construction of the medical device.

Going deeper, the general requirements are aimed at the safety and health of patients and at minimizing the risks associated with use. Any undesirable side-effect must constitute an acceptable risk when weighted against the performances intended [4].

On the other hand, the organization of the second section is different, and it is divided into seven groups [4]:

- *Chemical, physical and biological properties:*
  particular attention must be paid to the choice of the materials and compatibility between materials used and biological tissues, cells and body fluids.
- *Infection and microbial contamination:*
  the devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. Procedures for the sterile and non-sterile devices with a particular attention to the packaging systems for non-sterile devices.
- *Construction and environmental properties:*
  procedures for safety performances and minimization of risks related to their characteristics and the environment.
- *Devices with a measuring function:*
  precision and accuracy of analytical measuring devices.
- *Protection against radiation:*
  rules for devices intended to emit radiation and related instructions for use.
- *Requirements for medical devices connected to or equipped with an energy source:*
  devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use and to minimize the risks. Attention to the protection against electrical risks [4].
- *Information supplied by the manufacturer:*
  Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the details on the label and the data in the instructions for use [4]. The label must bear the name and address of the manufacturer.

This structure is valid for both the directives 93/42/EEC and 90/385/EEC with a particular attention to a better subdivision of the groups and reinterpretation of some points from 93/42/EEC Directive.

The essential requirements are therefore specifications to which the manufacturer must comply in order to market his products especially according to their safety.

2.1.2 Classification

The medical devices classification occupies an important role within Directive 93/42/EEC, unlike 90/385/EEC on the active implantable medical devices, because this Directive regulates already a risk class of devices.
The classification content is addressed in Article 9 and widely discussed in Annex IX of 93/42/EEC Directive.

As mentioned earlier in Chapter 1, the world of medical devices appears to be large and full of variations in the potential severity of harm to the patient or user. For this reason, in order to better analyse them with their specifications, the medical devices are subdivided into four categories, Class I, IIa, IIb and III, based on the level of the risk with the relative conformity assessment and procedure. These classifications are based on the intended purpose of the device, as well as the duration of contact with the body and the degree of invasiveness [15]. The degree of risk and invasiveness increases as the class to which they belong increases, i.e. from class I to III, as described in Figure 6, starting from green colour for Class I to arrive at red colour for Class III. Green colour points out a class of medical devices with less criticality and non-invasiveness. Afterwards, enhancing the class, increase also risk degree with medical devices of Class II which are divided in Class IIa (yellow circle) intermediate risk and Class IIb (orange circle) medium-high risk. The classification ends with class III high-risk devices. This class includes implantable devices, those that contain drugs or

animal derivatives and some devices that interact with vital organs [4]. Some examples for each class are reported in Figure 6.

The entire Annex IX "CLASSIFICATION CRITERIA" deals with the classification criteria and rules, divided into three sections [4]:

- *Definitions for the classification rules:*
  it collects a series of definitions such as duration, invasive and non-invasive device, reusable surgical instrument, active and therapeutical medical device and active device for diagnosis.
  Especially the duration is sectioned as Transient, continuous use for less than 60 minutes, Short Term, continuous use for not more than 30 days and Long Term, continuous use for more than 30 days [4].
- *Implementing rules:*
  application of the classification rules shall be governed by the intended purpose of the devices [4]. When a device is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices.
- *Classification:*
  subdivision of medical devices into four classes of belonging Class I, IIa, IIb and III, according to 18 rules.

Focusing on this last section, the 18 rules drawn up in section three, have been split according to non-invasive devices (Figure 7), invasive device (Figure 8), active devices and special rules (Figure 9).

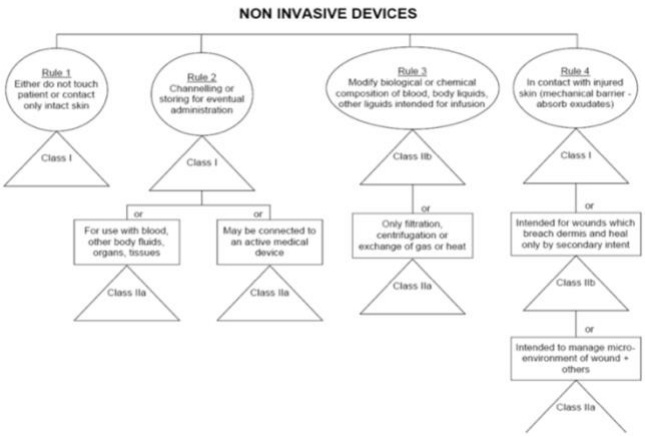


Figure 7: Rules and Classification of non-invasive devices [14].

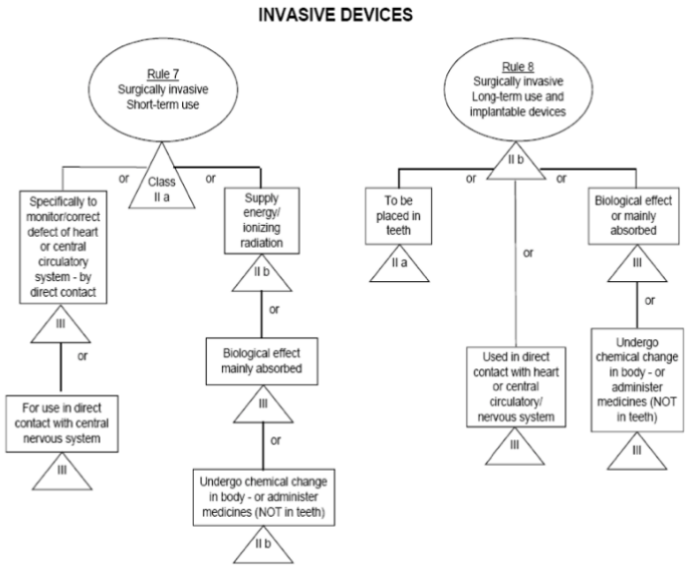


Figure 8: Rules and Classification of invasive devices [14].

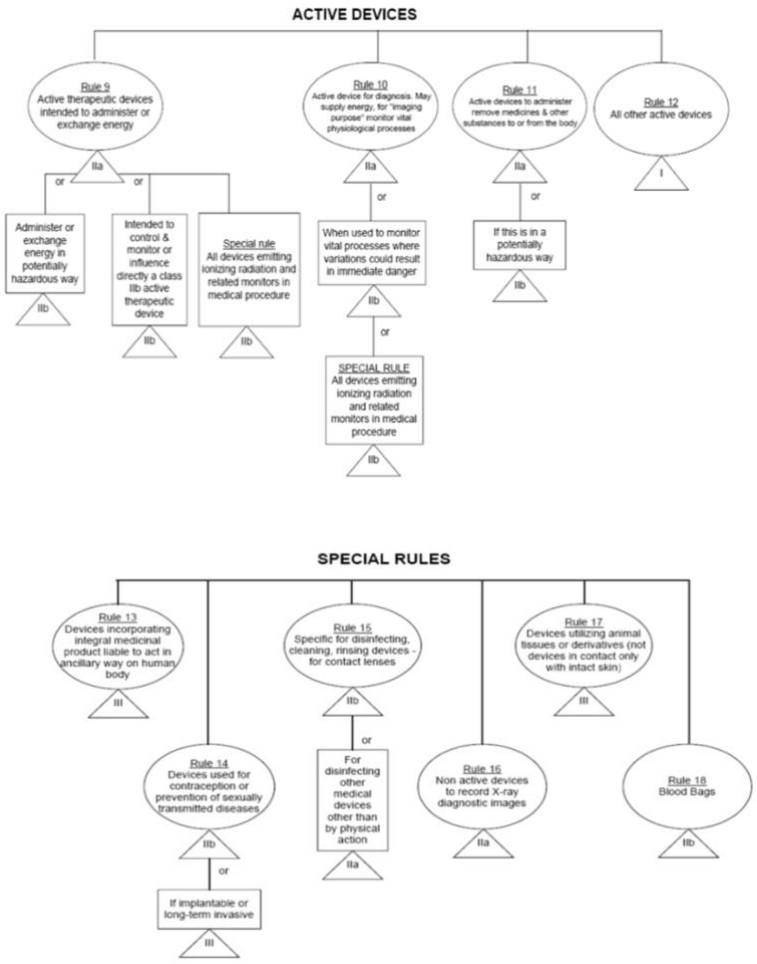


Figure 9: Rules and classification of active devices (Above), Special Rules (Below) [14].

Special rules include guidelines for the classification of the all the devices used for the contraception or prevention of the transmission of sexually transmitted (Class IIb), all devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product (Class III), all devices intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate, hydrating contact lenses (Class IIb) [4].

A summary of the entire classification is shown in Table 1, in which it is possible to find the breakdown by classes, the level of risk of each class, an example of a medical device, the conformity assessment and approval by a Notified Body

(NB). This latter in an organization designated by a Member State with the purpose to ensure the conformity assessment procedures. So, the manufacturer initially determines the classification of their device and then the NB approves this classification. In the case of NB and manufacturer disagree on the classification of the device, either party can refer the case to the competent authority for a final decision [4,15].

Table 1: Assessment routes according to the medical device classification [15].

Medical device class	Level of risk	Example	Type of assessment	Application to a notified body to approve the declaration
Class I *Excluding sterile products and/or those with a measuring function*	Low	Non-sterile gloves	Technical documentation + EC Declaration of conformity (Annex VII of the MDD)	No (Self-certification)
Class I *Sterile products and/or those with a measuring function*	Low	Thermometers	Same requirements as Class I non-excluding sterile products and/or those with a measuring function + manufacturer's choice from the following options: 1. Examination and testing of each product or homogenous batch of products (Annex IV of the MDD) 2. Audit of the production quality assurance system (Annex V of the MDD) 3. Audit of final inspection and testing (Annex VI of the MDD) 4. Audit of the full quality assurance system (Annex II of the MDD)	Yes
Class IIa	Moderate	Sterile needles	Audit of the full quality assurance system (Annex II of the MDD) or Same requirements as for Class I devices excluding sterile products and/or those with a measuring function + either option 1, 2 or 3 above	Yes
Class IIb	Moderate	Surgical meshes	Audit of the full quality assurance system (Annex II of the MDD) or Type examination (Annex III of the MDD) + either option 1, 2 or 3 for Class I sterile products and/or those with a measuring function	Yes
Class III	High	Peripheral stent	Audit of the full quality assurance system (Annex II of the MDD) or Type examination (Annex III of the MDD) + either option 1 or 2 for Class I sterile products and/or those with a measuring function	Yes

EC: European conformity; MDD: Medical devices Directive

2.1.3 Market placing and EC declaration of conformity

The market placing of any medical device is subjected to strict compliance with the essential requirements prescribed by Directive 93/42/EEC. The article 2 is referred to the above for both the regulations described (93/42/EEC and 90/385/EEC), according to which a medical device can be placed on the market and put into service only if it does not compromise the safety and health of patients, users and third parties, if it is subjected to adequate maintenance and if it

will be used in accordance with its intended purpose. Since the devices meet the essential requirements of Article 3 described above, they must bear CE conformity marking at the time of market placing (Figure 5) [4]. The CE marking, explained in Article 17 and Annex XII, must be affixed in a visible, legible and indelible manner on the devices in question or on their sterile wrapping accompanied by the code number of the NB responsible for the application [4]. The same NB which carries out examinations and tests necessary to verify the conformity of the product with the requirements of the directive, both by checking and testing each product, and by testing the products on a statistical basis [4]. Therefore, the CE verification is an adhesive procedure with which the manufacturer and his authorized representative, established in the community, guarantees and declares that the products comply. Once the CE mark has been applied, the manufacturer undertakes to prepare an EC declaration of conformity. The declaration of conformity is not a formal declaration but an assumption of responsibility which is in any case indispensable for the CE marking of the product and for its placing in the market. With this document, the manufacturer assures and declares that the product complies with the provisions of the directive [4]. Usually, there is no mandatory format and the contents of the declaration of conformity are indicated in a generic way.

In both directives, it is handled in Annex II for full quantity assurance system, in Annex V for production quality assurance, in Annex VI for product quality assurance and general information in Annex VII.

The minimum information contained in it relates to the quality system, i.e. the name and address of the manufacturer or the authorized representative issuing the declaration, all the necessary information regarding the product, regulatory documents performed, date of issue of the declaration, name and identification number of the NB and name and address of the person who keeps the technical documentation, CE label and instructions for use, for design and manufacturing schemes.

As described in Table 1, for each class of medical devices, the 93/42/EEC Directive indicates different procedures for certifying compliance with the essential requirements. For example, non-sterile and non-measurable class I medical devices do not require the intervention of a NB, but the manufacturer can affix the CE marking after having drawn up a declaration of conformity to the aforementioned requirements. For all other devices, belonging to the other classes, the action of a NB is envisaged, which implements the necessary conformity assessment procedures.

As described in Table 1, for each class of medical devices, the 93/42/EEC Directive indicates different procedures for certifying compliance with the essential requirements. For example, non-sterile and non-measurable class I medical devices do not require the intervention of a NB, but the manufacturer can affix the CE marking after having drawn up a declaration of conformity to the aforementioned requirements. For all other devices, belonging to the other classes, the action of a NB is envisaged, which implements the necessary conformity assessment procedures.

The entire procedural process that leads the manufacturer to acquire the long-awaited CE mark, an indispensable requirement for placing the device on the market, is described in Figure 10.

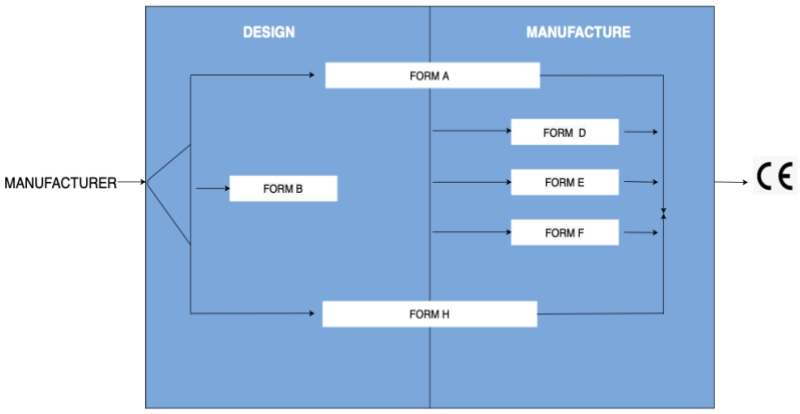


Figure 10: Flow diagram of the procedures for the conformity evaluation [1].

From Figure 10, it is possible to notice that the entire conformity evaluation includes both product design and manufacturing aspects. The forms are six, each of which represents an annex in the 93/42/EEC Directive, as follows [4]:

• Annex II is the "EC DECLARATION OF CONFORMITY (Full quality assurance)".

• Annex III is the "EC TYPE-EXAMINATION"

• Annex IV is the "EC VERIFICATION"

• Annex V is the "EC DECLARATION OF CONFORMITY (Product quality assurance)

• Annex VI is the "EC DECLARATION OF CONFORMITY (Product quality assurance)".

• Annex VII is the "EC DECLARATION OF CONFORMITY".

Some of the forms concern manufacturing and only form B is dedicated for the design product (Figure 10). They can be combined with each other in order to define complete conformity assessment procedures which will have to be related to both design and production. Below are the forms with the relative annexes of reference:

- Annex II= FORM H;
- Annex III= FORM B;
- Annex IV= FORM F;
- Annex V= FORM D;
- Annex VI= FORM E;
- Annex VII=FORM A.

Each annex contains the documentation that the manufacturer must prepare, the obligations that must be implemented, any declarations of conformity that must be drawn up and the certifications that must be requested from the NB to acquire the coveted CE marking.

Figure 11, Figure 12, Figure 13 and Figure 14 emphasize the conformity assessment routes for each class of medical device and the relative manufacture's choice of conformity route.

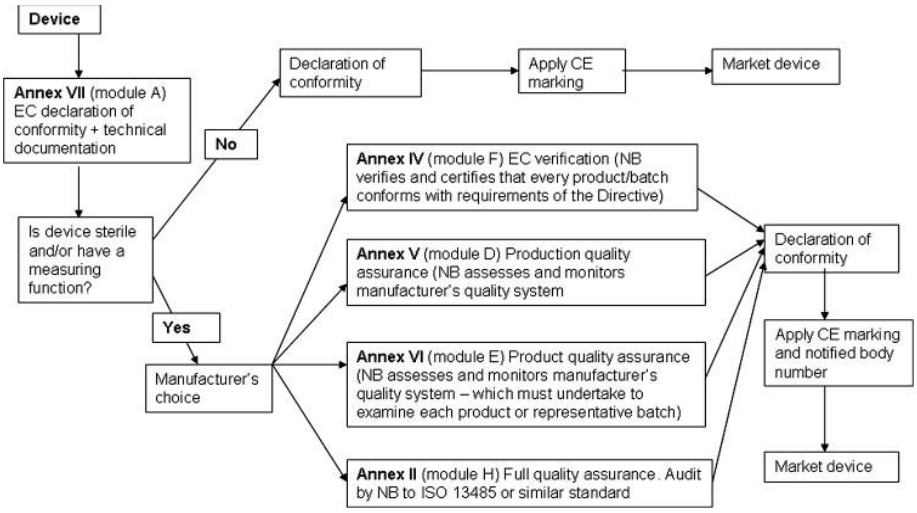


Figure 11: Class I conformity assessment procedures [16].

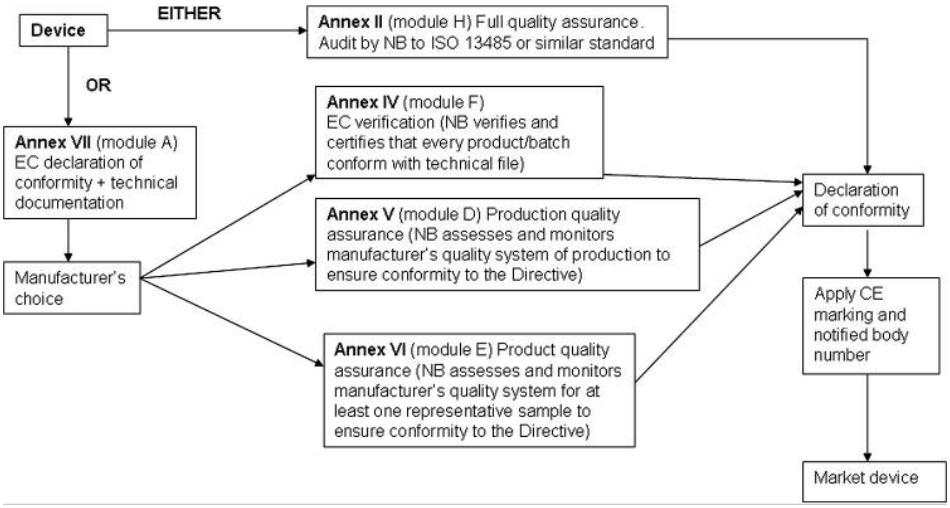


Figure 12: Class IIa conformity assessment procedures [16].

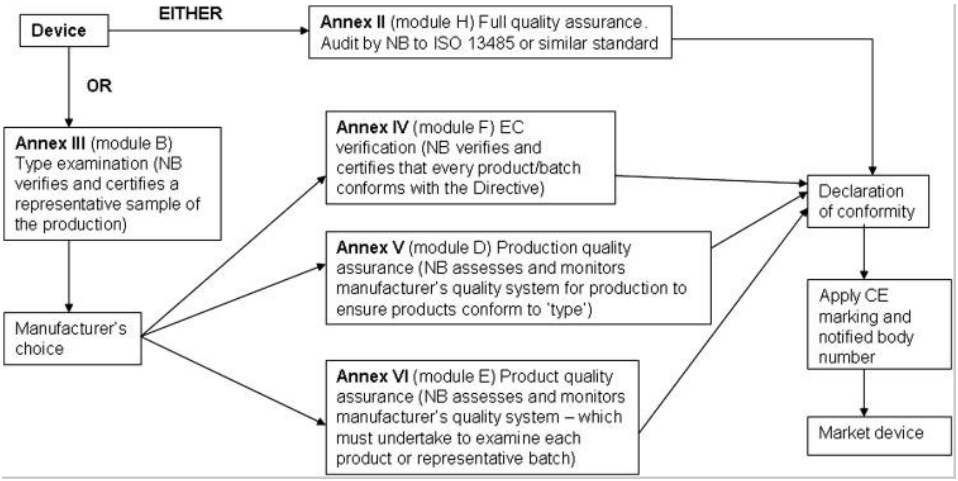


Figure 13: Class IIb conformity assessment procedures [16].

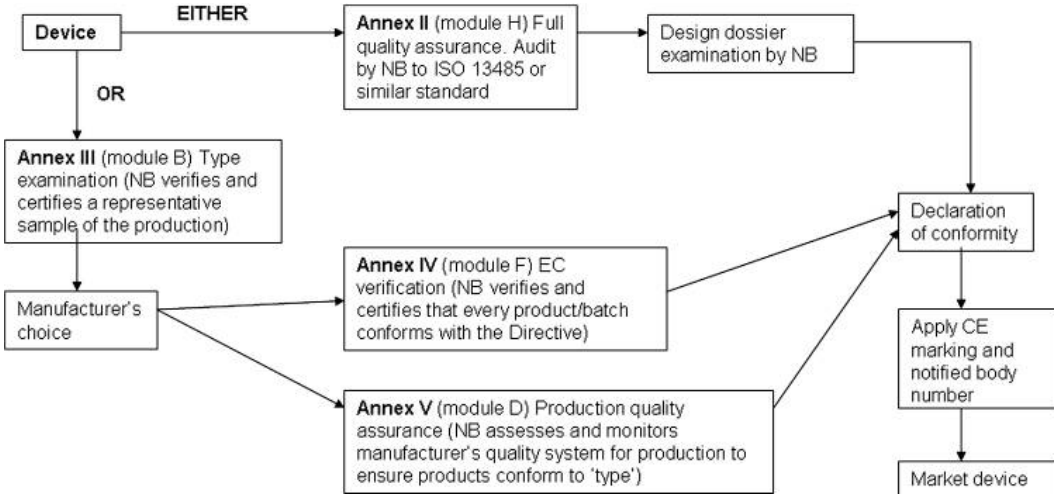


Figure 14: Class III conformity assessment procedures [16].

The modules that are reported in the Figures 11,12,13 and 14 are related to forms mentioned above.

2.1.4 Medical device vigilance systems

The main purpose of the medical device vigilance system is to improve the protection of the health and safety of patients and of users in order to avoid

incidents. According to the "Attuazione della Direttiva 93/42/CEE concernente i dispositivi medici", from Article 9, Article 10 (93/42/EEC) and Article 8 (90/385/EEC), an incident is defined as *"any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health"* [4,11,17]. If a public or private health worker detects an accident during the exercise, involving a medical device, shall notify the manufacturer or the supplier, who will immediately inform the Ministry of Health of the accident that has occurred [17]. Once the communication has been received, the Ministry of Health will carry out an assessment and inform the European Commission and other Member States about the measures taken to minimize the recurrence of incidents.

Therefore, the supervisory system is based on a close cohesion between manufactures, National Competent Authorities, the European Commission, NB and users. A first notification phase is up to the manufacturer with the collaboration of health workers, final users and Ministry of Health, following an investigation phase by the manufacturer. The final investigation phase, including any corrective actions, are assessed by the Ministry possibly in collaboration with the manufacturer [1]. The entire flow of vigilance reports on medical devices is shown in Figure 15.

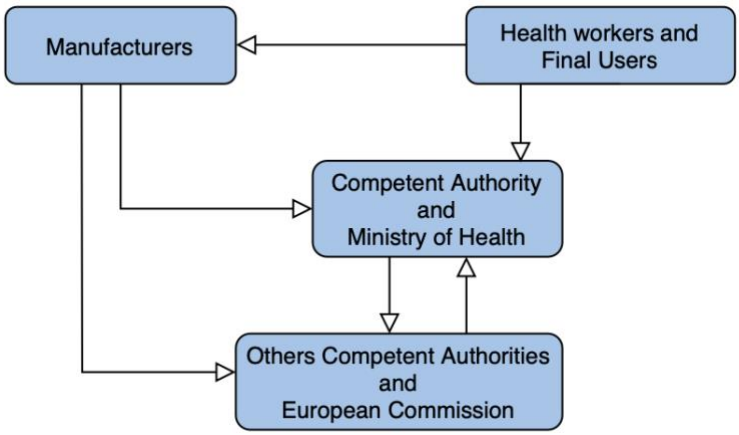


Figure 15: Flow of vigilance reports on medical devices [1].

Ascertained the defect of the device, the corrective action implemented by the figures prepared for this purpose can be limited to the withdrawal of the medical device, to a further modification of the medical device, changes to the labelling, to the instructions for use, components or manufacturing processes [18].

A particular focus on the number of alerts of accidents and lacking accidents on medical devices, notified by the Ministry of Health, was carried out in Italy region by region (Figure 16).

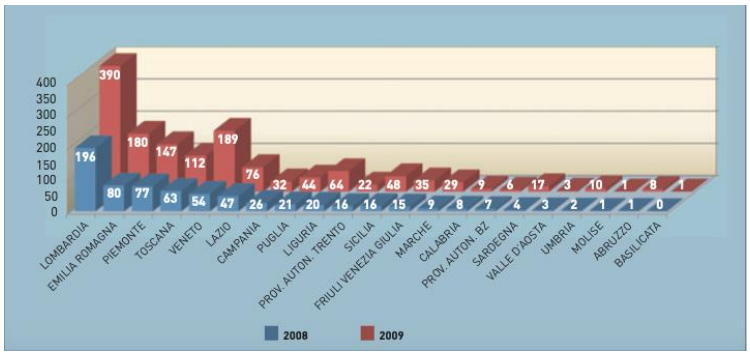


Figure 16: Incidents alerts in Italy reported by the health workers in 2008/2009 years [1].

Figure 16 is composed by horizontal axis in which are reported all the Italian regions and on the vertical axis is reported the quantitative scale of the accidents fixed in a measurement range from 0 to 400 incidents. The red and blue histograms record the number of the incident alerts in Italy in 2009 and 2008 years respectively. A comparative assessment of the number of alerts shows a general increase in 2009 in almost all regions and in particular in those in which the contact persons for supervision are in greater number. The Lombardy region in 2009 turned out to be the region with the greatest accidents detected in the field of medical devices (Figure 16).

In order to avoid a year-on-year increase in accidents on medical devices and thus to ensure greater safety, the manufacturer is obliged to update the risk management procedures on the basis of the information collected during the

marketing phase, taking into account also the complaints from the users. From these assumptions, the manufacturer can highlight a possible dangerousness of device and voluntary undertake corrective actions based on the diffusion of safety notice to users or a recall from the market. The procedure, also in this case, ends with the figure of the Ministry who assesses the criticality of the situation and decides to operate.

2.1.5 Clinical evaluation

Clinical evaluation is a methodological system based on the collection and analysis of clinical data relating to a device with the aim of evaluating its safety, functionality and clinical benefits for which it was designed. It's a procedure indispensable in order to ensure compliance of the device with the essential requirements for safety and to correctly conduct risk analysis. In fact, it is required for the initial CE marking [19]. It is a process conducted during the life cycle of the medical device, generally performed during the development step.
The provisions on the clinical evaluation are listed in Annex X of both directives. According to this annex, the manufacturer must follow a methodologically valid procedure which is represented by a critical evaluation of the scientific literature or an evaluation of the results of clinical investigations conducted on the performance of the device. These clinical investigations have two aims: evaluate the conformity of the device performance in order to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device [4]. The investigations must be performed under the responsibility of a medical practitioner or another authorized qualified person in an appropriate environment who at the end of the procedure presents a written report about the critical evaluation of all the data collected during the clinical evaluation [4].

The procedure by which the manufacturer can carry out clinical investigations are different. For example, in the case of devices falling within Class III and

implantable and long-term invasive devices falling within Class IIa or IIb, the manufacturer may commence the relevant clinical investigation at the end of a period of 60 days otherwise in the case of devices differ from the above mentioned, Member States may authorise manufacturers to commence clinical investigations immediately after the date of notification [4].

So, the clinical evaluation, composed by a series of clinical investigations, is necessary and important because it ensures that the evaluation of the safety and performance of the device is based on clinical evidence sufficient for the entire life span of the medical device on the market.

2.2 Issues related to 93/42/EEC and 90/385/EEC Directives and look at the future European Medical Device Regulation (MDR) 2017/745

Since 1990 with the 90/385/EEC Directive concerning the implantable active device and the MDD 93/42/EEC that the Europe-wide medical device has been regulated. Up to now MDD constitutes the only document that manufacturers, competent authorities and NB rely on in order to trade a medical device.
The experience gained since 1993 with the MDD turns out to be extremely positive but with the onset of the new decade and scandals emerged against patients, a review of the whole directive by all the stakeholders was deemed appropriate. As reported in "EDITORIAL" examples of scandals are embodied by the breast implant scandal, controversy with regard to metal-on-metal hip replacements and complications after vaginal mesh implantation [20]. From these facts it can be observed that Europe-wide medical device had to be revised keeping always the main goal that is to improve the clinical safety of medical devices on the market in Europe and to increase the credibility and reputation of the oversight system [20].
In this regard, the Commission of the European Communities met on December 22, 2005 to discuss about a review of the 90/385/EEC and 93/42/EEC Directives [21]. The proposal, presented to the European Commission, was articulated into several points. The changing did not concern only Article 11 (Evaluation of the

conformity) of MDD but also the other aspects of the entire directive that were a source of concern or that are likely to be improved [21]. The points discussed and which today constitute the new features are:

- Evaluation of conformity.
- The suitability of clinical data for all classes of device.
- The role of the NB, in terms of their ability to carry out the tasks assigned to them.
- Greater transparency as regards the approval of devices.

The modification regards also the 90/385/EEC Directive on the implantable active device in order to be aligned with the other directives on medical devices.

This process of change and revision of the Directives is culminated in the publication of the new European medical device regulation (MDR) 2017/745 in May 2017. In the same period was published the new European medical device regulation 2017/746 concerning in-vitro medical devices. These regulations, differ from Directives, become immediately law in all the Member State in Europe [20].

Nowadays, 2020, precisely in May 2020, after three years of transition from MDD to MDR, this MDR it should have gone into effect as a new reference point in the field of medical devices, but the ongoing global pandemic of COVID-19 has been postponed to May 2021.

The certificated medical devices already on the market, according to the MDD, will remain valid for a further four years until May 2024 [21].

New features, new figures and other important aspects will be discussed in next chapter.

Chapter 3

NEW EUROPEAN MEDICAL DEVICE REGULATION (MDR) 2017/745

The aim of this chapter is to describe the main points of the new European Medical Device Regulation (MDR) 2017/745 that, should have entered in force in May 2020, subsequently postponed in May 2021 due to global Covid-19 pandemic.

3.1 MDR General information and structure

As mentioned in Chapter 2, the origin of the new European medical device regulation (MDR) comes after failures and adverse effects associated with certain implants, fraudulent use of non-medical grade silicone in breast implants [22] and other episodes of scandal. These facts lead the European Community to a 'revision', of the current system for medical device regulation in Europe [22]. Therefore, due to these unpleasant incidents and an increased number of medical devices in these recent years, two new regulations should have entered in force in Europe May 5, 2020 with the aim to reinforce the level of safety and health:

- *The Medical Device Regulation (MDR)* 2017/745 concerning the medical devices, amending Directive 2001/83/EC, Regulation (EC) n.178/2002 and Regulation (EC) n.1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC [23].
- *In vitro diagnostic medical device Regulation (IVDR)* 2017/746 concerning the medical devices and repealing Directives 98/79/EC, 93/42/EEC [4] and Commission Decision 2010/227/EU.

This thesis is focused on the MDR 2017/745 that, concerning the medical devices, redesigns a robust, transparent, predictable and sustainable regulatory framework for medical devices, replacing the previous 93/42/EEC Directive.

The new MDR 2017/745 consists of 123 Articles, divided in 10 chapters and in XVII Annexes. In these 10 chapters, the articles are subdivided according to the topics covered, that represent a key-content of the regulation.
It will come into force definitively in May 2021 with specific objectives:

- It ensures the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users.
- It sets high standards of quality and safety for medical devices [23].

In order to improve the health and safety of patients and users, some key elements of the current regulatory system have been strengthened. These main points will be discussed in the next sections.

3.1.1 Scope and Definitions

The first chapter "SCOPE AND DEFINITIONS" of the MDR includes four articles. Below are reported only some of the relevant news. The Article 1 *"Subject matter and scope"* specifies the Regulation scope, or rather it establishes the rules concerning the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices in the European Union [23]. Furthermore, it defines the subject matter to which it will be apply.
The Regulation dedicates for all medical devices, accessories of medical devices and products listed in Annex XVI of this MDR. Contrary, the Regulation does not apply to in-vitro diagnostic medical devices, cosmetic products, advanced therapy medical product and others that are listed in the paragraph 6 of Article 1 [23].

Article 2 *"Definitions"* rewords the definition of a medical device. It starts from the definition of a medical device written in Chapter 1 and it adds a new part, as follows:

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

-devices for the control or support of conception.

- products specifically intended for the cleaning, disinfection or sterilization of devices [23]. This definition sets a scope expansion of the Regulation respect to the medical devices. It includes devices that have not a medical intended purpose, such as coloured contact lenses, cosmetic implant devices, materials and devices intended for the prediction and prognosis of disease.

Besides the general definition of medical device, Article 2 includes 71 definitions useful in the medical device sector. A series of definitions are used in the next paragraph and explained as follows:

- *Manufacturer*. A natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark [23]. This figure is very relevant for the devices marketing. It will be discussed in the next paragraph.
- *Authorised representative* is defined as any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation [23].
- *Importer* means any natural or legal person established within the Union that places a device from a third country on the Union market [23].
- *Distributor* means any natural or legal person in the supply chain, other than the manufacturer or the importer, who makes a device available on the market, up until the point of putting into service [23].

3.1.2 Making available on the market and putting into service of devices, obligations of economic operators, CE marking and free movement

The second chapter "MAKING AVAILABLE ON THE MARKET AND PUTTING INTO SERVICE OF DEVICES, OBLIGATIONS OF ECONOMIC OPERATORS, CE MARKING AND FREE MOVEMENT" develops from article 5 until article 24.

Underlying the *"placing on the market and putting into service",* Article 5*,* a medical device must be supplied and properly installed, maintained, used in accordance with its intended purpose and satisfy the general requirements about safety and performance, described in Annex I [23]. Annex I "*General Safety and Performance Requirements (GSPR)"* involves more specific and detailed requirements than the essential requirements of MDD. Examples are the labelling, the environmental risk and risk management.

The medical devices manufactured and used only in the health institution, established in European Union, must be integrated with a documentation concerning the manufacturing process, the design and performance data of the devices, including the intended purpose, in order to ascertain the GSPR [23]. At the end the manufacturer draws up a technical file of the device.

For what concern the label, Article 7 *"Claims"* states that, in the labelling like instructions for use, it shall be prohibited to use text, names, trademarks, pictures and figurative or other signs that may mislead the user or the patient with regard to the device's intended purpose, safety and performance [23].

In Article 10 *"General obligations of manufacturers"* are defined different steps that must be complied by the manufactures to place their devices on the market.

This figure is called to draw up and keep up technical documentation for those devices. The technical documentation is described in Annex II *"Technical documentation"* and it includes [23]:

- Device description and specification, including variants and accessories.

- Information to be supplied by the manufactures.
- Design and manufacturing information.
- General safety and performance requirements.
- Benefit-risk analysis and risk management.
- Product verification and validation, in particular pre-clinical and clinical data.

Moreover, the manufactures are responsible for the quality management system. In fact, they ensure that the device is accompanied by the information concerning general requirements, they manage the risk management, they provide the necessary documentation to demonstrate the conformity of the device and they shall implement and keep up to date the post-market surveillance system in accordance with Article 83 *'Post-market Surveillance'* [23], novelty in MDR.
Manufacturers not established in the European Union are substituted by a new figure called *"Authorised representative",* explains in Article 11 and defined previously.

After the general obligations of manufacturers, *"General obligations for importers",* Article 13 and *"General obligations of distributors",* Article 14, are listed in the new regulation in order to place a device on the market.
Each figure has specific steps to follow.
Distributors steps:

- The device has been CE marked and the EU declaration of conformity of the device has been drawn up [23].
- A manufacturer is identified and that an authorised representative in accordance with Article 11 has been designated by the manufacturer [23].
- The device is labelled in accordance with this Regulation and accompanied by the required instructions for use [23].
- where applicable, a Unique identification device (UDI) has been assigned by the manufacturer in accordance with Article 27 [23].

Importers steps:

- The device has been CE marked and the EU declaration of conformity of the device has been drawn up [23].
- The device is accompanied by the information to be supplied by the manufacturer in accordance with Article 10 [23].
- For imported devices, the importer has complied with the requirements set out in Article 13 [23].
- UDI code [23].

Sometimes the manufacturers obligations are applied to importers, distributors or other persons. The cases where it occurs are listed in Article 16 *"Cases in which obligations of manufacturers apply to importers, distributors or other persons"* [23].

A major figure in this MDR is embodied by "*Person responsible for regulatory compliance"* in Article 15. Within the manufacturer's organization, is named at least a person responsible for regulatory compliance who possesses the required expertise in the field of medical devices. The expertise shall be demonstrated from a certified qualification, such as university degree or certificate, and with four years of professional experience in regulatory affairs or in quality management systems relating to medical devices. This figure shall ensure that:

- The conformity of the devices is appropriately checked, in accordance with the quality management system under which the devices are manufactured before a device is released [23].
- The technical documentation and the EU declaration of conformity are drawn up and kept up to date [23].
- The post-market surveillance obligations are complied with in accordance with Article 10 [23].
- The reporting obligations referred to in Articles 87 to 91 are fulfilled [23].
- In the case of investigational devices, the statement referred is issued [23].

This figure in mainly introduced in this Regulation to ensure better traceability of devices and to avoid cases of fraud.

Another innovative feature, that the manufacture must be provide when he manages with implantable device, is an implant card. It contains the device name, serial number, UDI code, device model, info about the device identification, as well as the name, address and website of the manufacturers [23]. Also, any other information about the lifetime of the device and any necessary follow-up [23]. These info are available in the Article 18 *"Implant card and information to be supplied to the patient with an implanted device"* [23].

As it occurred with the MDD, the *"free movement"*, Article 24, always happens after the conformity declaration of the device. The *"EU declaration of conformity"*, Article 19, is coupled with Annex IV *"EU declaration of conformity"* which contains the useful information to draw up the declaration. At the same time, the *"CE marking of conformity",* Article 20 with Annex V is the same and it applied according to MDD (Figure 5).

The entire process to obtain the CE mark and then market in Europe is described in Annex II of this thesis.

3.1.3 Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance and European database on medical devices

The third chapter "IDENTIFICATION AND TRACEABILITY OF DEVICES, REGISTRATION OF DEVICES AND OF ECONOMIC OPERATORS, SUMMARY OF SAFETY AND CLINICAL PERFORMANCE AND EUROPEN DATABASE ON MEDICAL DEVICES" involves from Article 25 until Article 34.

The third section of this Regulation brings some news about the identification and traceability of medical devices. Starting from Article 25 *"Identification within the supply chain"*, in which a real chain of control and traceability is created between distributors or importers and manufacturers or mandators defines as 'economic operators'.

In order to create this traceability network, the European Commission has drawn up three innovations:

- A *"Medical device nomenclature",* Article 25, internationally recognised and available free of charge to the manufacturers, stakeholders or for other legal persons [23]. It's a tool used by the manufactures when registering their medical devices in the European database.
- An *"Unique Device Identification (UDI) System"*, Article 27 and Annex VI [23].
- An *"European database on medical devices ('Eudamed'),"* Article 33.

UDI is a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market [23].

Figure 17: Unique Device Identifier (UDI) [24].

It includes two parts: an UDI device identifier ('UDI-DI'), unique numeric or alphanumeric code for model of device and it is also used as "access key" in UDI database [23]. It helps to distinguish if medical device is for example an artificial limb or a plaster. The second part is an UDI production identifier ('UDI-PI') that identifies the unit of device production and if applicable the packaged devices, for example it can contains the production date, the product batch etc. This UDI code

is placed on the label of the device or on its packing in text format or bar code (Figure 18) and the entire UDI system is controlled and assigned by an 'issuing entity' at least 10 years [23]. These entities are embodied by a global organizations and standardizing bodies that define rules for the identification. In Italy, for example, the issuing entity is embodied by the GS1, which is the only Italian organization authorized by the European Commission to support companies with UDI codes [25].

Figure 18: Zoom-in of an UDI code on a medical device [26].

All these UDI codes are collected with a database, *"UDI database"*, Article 28, that

makes them available to share the information provided by the manufactures, freely.

Hence, before placing the device on the market, the manufacture assigns not only the well-known CE mark but also a Basic UDI-DI to the device, thus supplying a *"Registration of devices",* Article 29. Same registration ups to the economic operators, manufactures, authorised representatives and importers with an electronic system, Articles 30 and 31.

As mentioned previously, Article 27 on UDI, is coupled with the Annex VI *"Information to be submitted upon the registration of devices and economic operators in accordance with articles 29 and 31, core data elements to be provided to the UDI database together with the UDI-DI in accordance with articles 28 and 29 and the UDI system",* which articulated in 3 parts:

- Part A: the manufacture or the authorised representative provide the information relating to the economic operators (name, address, type etc)

and the information relating to the device (Basic UDI-DI, risk class, presence of tissues or cells etc) [23].

- Part B: the manufacturer provides to the UDI database the UDI-DI and information relating the manufacturer and the device [23].
- Part C: It defines the UDI system with a series of definition, such as *Automatic identification and data capture (AIDC)* as a technology used to capture the data with the use of barcodes, RFID, smart cards, *Basic UDI-DI* as the primary identifier of a device model, is the main key for records in the UDI database, *UDI carrier* means to convey the UDI using AIDC and it is placed on the label or on the device itself. Furthermore, the general principles of the UDI database, rules for specific device types [23] are specified.

It is important to emphasize that, whenever a change on the original performance safety and interpretation of data is made, it is necessary to change the UDI-DI code.

The third section ends with the introduction of the *"European database on medical devices (Eudamed)"* in Article 33. Eudamed has the aim to enhance the transparency, including the information for the public and for healthcare professionals with regard to the devices placed on the market, to the economic operators, to the notified bodies and about the clinical investigations, to facilitate the traceability and to enable the unique identification of devices within the internal market [22,23].The database includes different electronic systems relating to the registration of devices, of the economic operators, of the notified bodies, of the clinical investigations, on vigilance and post-market surveillance, UDI-database [23]. The entire structure is shown in Figure 19.

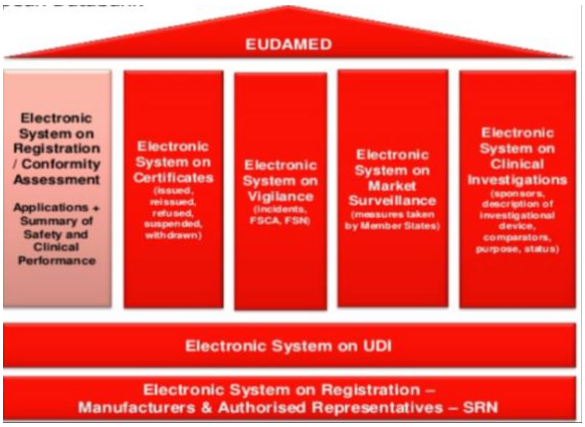


Figure 19: Eudamed database system [27].

As described in Figure 19, Eudamed is composed by seven modules; red blocks, excluding the roof, and the pink block that includes also the summary of safety and clinical performance written in a clear way and available to the public. The structure, by which the summary shall be draw up, is presented in Article 32, *'Summary of safety and clinical performance'*.

The electronic system on registration or the action registration module is available from December 1st, 2020, useful for EU and not-EU manufacturers, competent authorities and importers to register to the Eudamed themselves, to provide necessary information and to obtain Single Registration number (SRN). All the information is available on the website of the European Commission in the section Eudamed.

Specifically, the electronic system on vigilance should enable manufactures to report serious incidents and to support the evaluation of these incidents with the competent authorities [22].

The electronic system on the market should be a tool for the exchange of information between competent authorities [22].

Instead, the electronic system on clinical investigation should serve as a tool for the coordination between member states and to report serious adverse events and device deficiencies [22].

3.1.4 Notified Bodies

The fourth chapter "NOTIFIED BODIES" develops from Article 35 to Article 50. According to the definition in the Chapter 1, a Notified Body (NB) is a conformity assessment body [23]. This figure is already existing in 93/42/EEC Directive but in this new MDR highly redesigned and strengthened due to a negative episode occurred with a fake hip prosthesis. For this reason, that the European Commission has decided to reshuffle the cards by strengthening the rules on designation and monitoring of NBs [28]. The NBs have to ensure their confidentiality, independence, objectivity and impartiality [28]. They are not named to participate at any step of the medical device life. In order to achieve, in a good way, their requirements, NBs shall have permanent availability of sufficient administrative, technical and scientific personnel explained in Article 26 *'Requirements related to the notified bodies'* and Annex VII *'Requirements to be met by notified body'* [23].

The Regulation not only has amended the figure of the "classic" NB, but it introduces the figure of a "special" NB, specialized in high-risk medical devices (Class III or medical device with medicinal products). Those special NBs are represented by experts in clinical investigations or pharmacology and product specialists [28].

Regarding the NB designation, in Article 38 *'Application by conformity assessment bodies for designation'*, cooperate different figures. At the beginning, the NBs shall submit an application for designation to the **authority responsible to the NB**. This authority has the aim to set up and carry out the necessary procedures for the assessment, design and notify of conformity assessment bodies and to monitor these latter, Article 35 *'Authorities responsible for notified bodies'* [23]. The entire assessment team is shown in Figure 20.

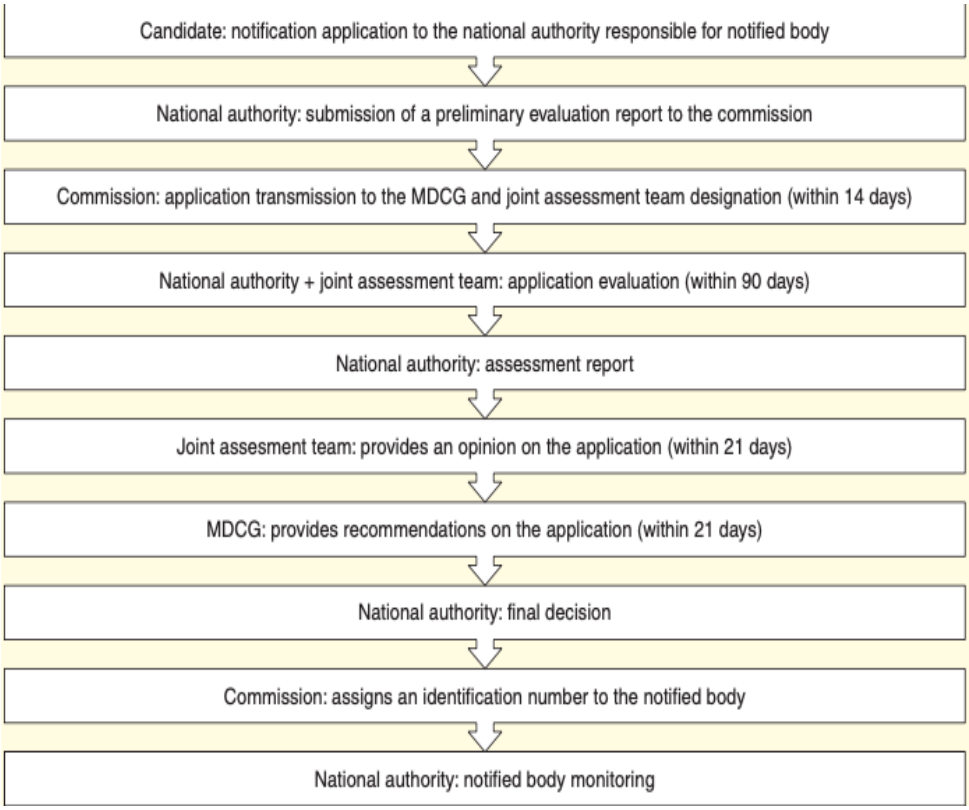


Figure 20: NB designation procedure according to the proposal for the new regulation on medical devices [28].

From Figure 20, the chain starts with the notification application from NBs to the **authority responsible to the NB**, who shall review the application and supporting documentation in accordance with its own procedures and shall draw up a preliminary assessment report to the Commission. The **Commission** transmits the application to the **medical device coordination group (MDCG)** and both, within 14 days, shall appoint a **joint assessment team** made up of three experts, one of them is the representative of Commission. The joint assessment team evaluates the conformity assessment activities and the types of devices subject of the application. Within 90 days, the joint assessment team together with the authority responsible to the NBs shall plan and conduct an evaluation of the NB. The assessment report is led by the authority responsible. Within 21 days, the joint assessment team shall document any remaining diverging opinions with respect to the assessment send them to the authority responsible for notified

bodies. Within 41 days, MDCG shall issue a recommendation with regard to the draft designation of the NB. The final decision rests with the authority responsible to the NB, who elaborates a final report with the results of the assessment, the confirmation and the implementation of the corrective actions, the diverging opinion and the recommended scope of designation. This report is sent to the Commission, MDCG and to the joint assessment team. At the end, the Commission assigns an identification number to the choose NB and makes available to the public a list of NBs in electronic notification tool within the database of notified bodies developed and managed by the Commission (NANDO) [23]. The NBs already notified in 93/42/EEC and 90/385/EEC Directives shall retain their identification number assigned. At the end, the authority responsible to the NB will supervise them.

All these steps are described from Article 39 *'Assessment of the application'* to Article 48 *'Peer review and exchange of experience between authorities responsible for notified bodies'* [23].

The structure described in Figure 20 is not followed by the special NBs that are under the responsibility of the European medicines agency [28].

Currently, in Italy, there are several NBs such as 'Bureau Veritas Italia S.p.a', 'TÜV Rheinland Italia srl', 'ISTITUTO SUPERIORE DI SANITA'' and others. They are involved in the CE marking assessment, ensuring safety and performance to the medical devices. Hence, the manufactures will have to turn to the designed NB to obtain the CE mark with a four digit-number that identifies the NB chosen (Figure 21).

Figure 21: CE mark with NB identifier.

Once the medical device has obtained the CE mark, NBs can annually audit manufacturers focusing on the post-market surveillance plan and on the quality management system also without announce [28]. All these activities to test the

conformity are performed under remuneration according to a list of fees established by the NBs, Article 50 '*List of standard fees'* [23].
To complete its activity, each NB shall issue a certificate to the manufacturer that identifies the device. A typical format of the certificate shall include the name and address of the NB and of the manufacturer, a unique number that identifying the certificate, the date of issue and of expiry, examinations and test performed and conclusions of the notified body's conformity assessment. Informations are listed in Annex XII *'Certificates issued by the notified body'* [23].

3.1.5 Classification and conformity assessment

The classification of medical devices is currently one of the key topics in the field of medical devices. Widely introduced in chapter 1 of this thesis and subsequently discussed in chapter 2, the new MDR also tackles the subject again, bringing some news about it.

The fifth chapter of the Regulation, called "CLASSIFICATION AND CONFORMITY ASSESSMENT", is divided into 2 sections [23]:

- Section 1 *'Classification'* deals exclusively of the new reclassification of medical devices and it includes only the Article 51 together with Annex VIII '*Classification rules'*.
- Section 2 '*Conformity assessment'* deals with the conformity assessment and it involves from Article 52 to Article 60 with Annexes IX, X, XI, XIII.

As regards the classification section, the proposal for the new regulation is based on the approach already defined in the previous MDD, i.e. based on the subdivision of medical devices into 4 classes, Class I, IIa, IIb and III, in accordance with Annex VIII of MDR.
The structure of the Annex VIII maintains the same organization of the Annex IX of 93/42/EEC Directive but with an enhance of rules, with 4 more rules:

- Rules 1-4: Non-Invasive devices
- Rules 5-8: Invasive devices.
- Rules 9-13: Active devices.
- Rules 14-22: Special rules.

The last new rules are aimed at devices that contain or are made up of nanomaterials with a particular attention to the potential risk (medium-III, low-IIb, negligible-IIa) with *Rule 19*; invasive devices with respect to body orifices to administer medicinal products to inhalation are classified in class IIa (*Rule 20*); substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed in class III or IIa *(Rule 21)* and active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management such as external automatic defibrillators *(Rule 22)* [23].

At the same time, the risk level remains the same that is shown in Figure 6 with the duration use, level of invasiveness and energy supply [29].

A particular consideration is computed on the medical devices of class I in which reusable, sterile and measuring devices are added, defining class Im, Is and Ir.
According to the MDD and MDR, a reusable surgical instrument is defined as: *'instrument intended for surgical use in cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or similar procedures, without a connection to an active device and which is intended by the manufacturer to be reused after appropriate procedures such as cleaning, disinfection and sterilisation have been carried out'* [23].

A conclusive recap based on the division of the medical devices, in line with the risk, is shown in Figure 22.

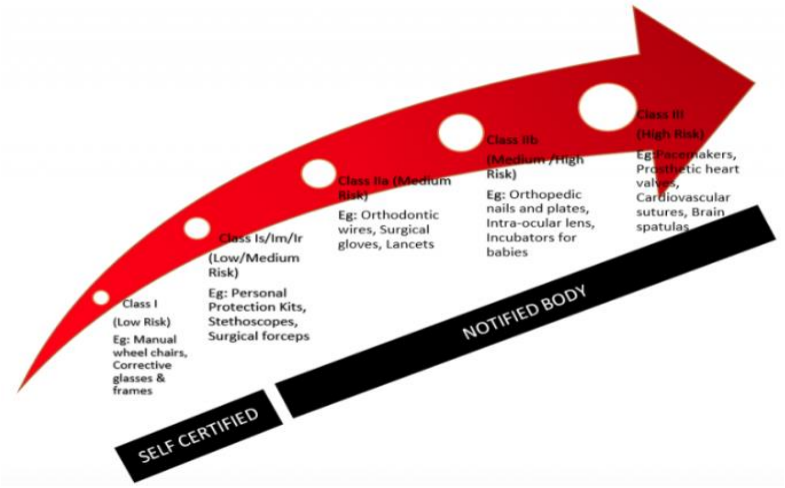


Figure 22: Medical devices classification according to MDR [29].

From Figure 22, it is possible to see the rise of the risk from class I to III with the red growing arrow.

The conformity assessment is discussed in section 2 of this chapter in different ways. The conformity evaluation shall be drawn up by the manufacturer who contacts the NB, and he chooses the appropriate procedure for your device, based on type and classification class. Higher is the risk and more accurate will be the analysis carried out by the NBs.
As can be seen in Figure 22, Class I can be self-certified for the CE compliance, following these steps [29]:

- Drafting of a Technical Documentation according to Annex II.
- Preparation of a Declaration of conformity according to Annex IV.
- Affixing of the CE marking according to Annex V.

On the contrary, medical devices of Class Ir, Is and Im will obtain the conformity assessment after the examination of the NBs, following these steps [29]:

- Confirm product as a medical device.
- Confirm product as a class Is, Im or Ir medical device.
- Confirm if the general safety and performance requirements have been met.

- Perform clinical evaluation.
- Prepare technical documentation.
- Request notified body involvement.
- Prepare instruction for use and labelling.
- Check compliance with general obligations for manufacturers as established in Article 10
- The draw of the EU Declaration of Conformity.
- Affix the CE marking.

Particular attention is dedicated to the procedure related to class III and IIb medical devices described in Annex X based on the quality management system (QMS) and on the assessment of the technical documentation. The NB, at least once every 12 months, verify the applied QMS and the post-market surveillance plan [23].

In addition, MDR sets the risk class from I up to III for the software useful in diagnosis or for therapeutic purpose (*Rule 11)* [23].

A summary framework is shown in Figure 23 in which are highlighted the Annexes and the chapters exploited to obtain the CE mark.

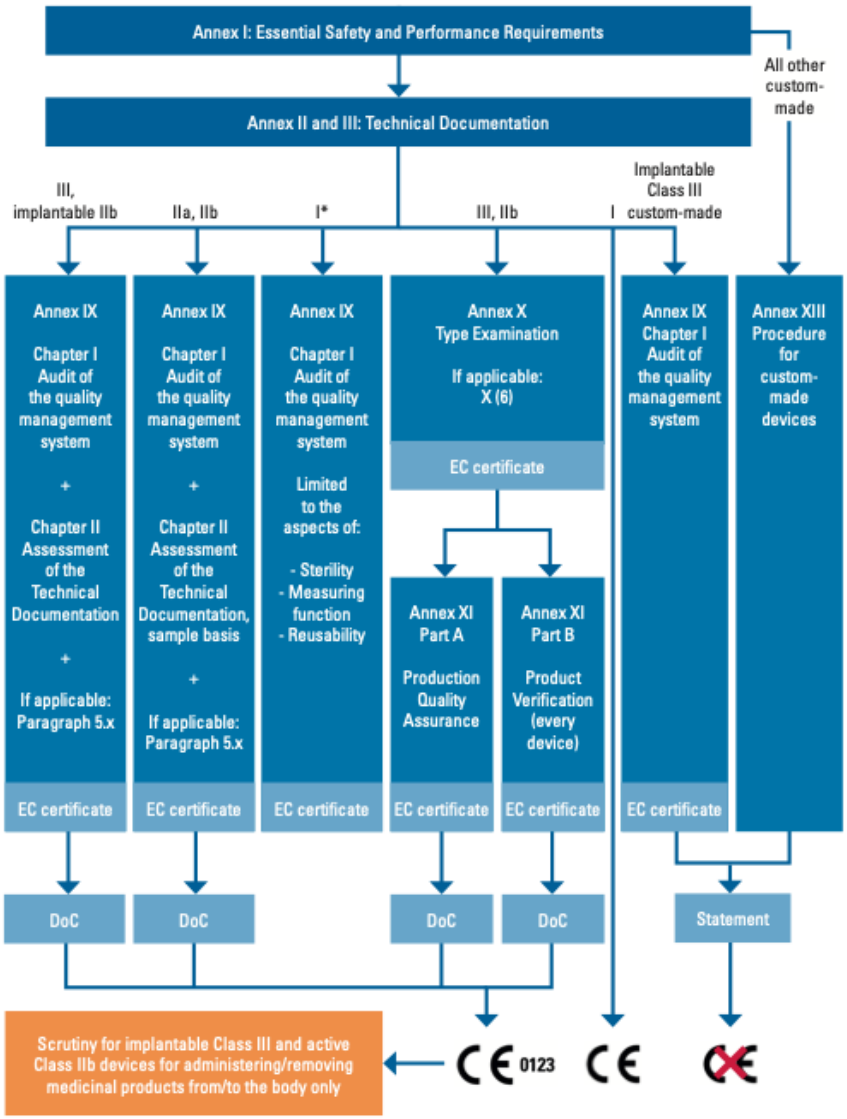


Figure 23: Conformity assessment diagram [30].

As described in Figure 23, the procedure starts with the examination of the essential safety and performance requirements according the Annex I. Once collected the information, the manufacturer draws up a technical documentation according to Annex II. This report does not cover the custom-made device that are directly subjected to the Annex XIII. After the technical documentation, the conformity assessment procure begins for all classes of devices in different ways. The aim of this method is to obtain the CE mark after an accurate declaration of

conformity (DoC). The only class that does not need the DoC and, directly, the manufacturer affixes the CE mark with the numbers because he does not need the NBs analysis, is class I except class Ir, Is and Im that are subjected to a regular analysis of conformity.
At the end, an additional step regards the Class III implantable devices and Class IIb products for administering or removing the drugs from the body, that are subjected to a further testing called *Scrutiny* from the NBs. In a scrutiny procedure, the NB checks the products for compliance and then creates a Clinical Evaluation Assessment Report (CEAR) [31]. This report is sent via European Commission to a panel of experts who decide on how to proceed on this product within 21 days [31].
Once the CE mark has been affixed, it is possible to perform the clinical evaluation.

3.1.6 Clinical evaluation and clinical investigations

The sixth chapter "CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS" involves from Article 61 until Article 82. It deals and strengthens the provisions related to the clinical evaluation and clinical investigations, referring to the Annex XIV-Part A *'Clinical evaluation'* and Annex XV '*Clinical investigations'*.

Although it has already been covered in chapter 2 of this thesis, it is appropriate to recall the meanings of clinical evaluation and clinical investigations.

According to the MDR, a clinical evaluation is a systematic and planned process to collect, assess and analyse the clinical data in order to verify the safety and performance of a medical device [23]. This process is defined as a wider source of data which includes, as described in Article 61 '*Clinical evaluation'* [15,23]:

- A critical analysis of the scientific literature related to the safety, performance, design characteristics and intended purpose of the device.
- All relevant scientific data available (technical data, preclinical data, etc.).
- A critical analysis of the results of the clinical investigations.
- An evaluation of the post-marketing data.

This entire clinical evaluation process with the different steps is depicted in Figure 24.

Figure 24: Main components of clinical evaluation of medical device according to MDR [32].

The four circles, inside the clinical evaluation, are not mandatory for all the devices. For example, according to the classification of a class IIa device, an introducer sheath, does not require a clinical investigations and only pre-clinical data would be enough for the clinical evaluation [15]. Different situation occurs with the class III and implantable devices that, under MDR, are subjected to a more or less specific clinical evaluation. In a detailed clinical evaluation, the manufacturer should demonstrate through a clinical investigation that its devices (ex: new peripheral stent) achieves the performance intended, safety and the expected clinical benefits [15]. At least one a year, the evaluation report must be update for these devices [23].

Instead, a less detailed clinical evaluation, is performed for the devices with already the CE mark affixed according to the MDD and valid until May 2024 [23,15], for devices produced by the same manufacture and with already the CE mark, for devices with a non-substantial modification (ex: device packing) and for

devices produced by another manufacturer with already CE mark and demonstrated to be equivalent to the previously marketed device also accepted by the NBs [23,15]. In this last scenario there is an interaction between the two manufacturers.

A relevant step in the clinical evaluation process is the clinical investigation.

In line with the MDR, a clinical investigation is any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device [23].

The clinical investigations shall be conducted, designed, authorised and recorded to establish and verify the intended use, the clinical benefits, performances and le safety of medical devices always protecting rights, safety, dignity and well-being of the subjects with seven Articles (from 62 to 69) and Annex XV *'Clinical investigations'* [23]. The investigations are performed by figure called *sponsor*, set by the European Union, who requests to carry out the clinical investigations by submitting an application for the clinical investigations, valid at least 10 years (Article 70) and coupled with a precise documentation (Chapter II-Annex XV) [23].

According to the definition in MDR, a sponsor is *any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation* [23].

The sponsors are mostly research organizations available to the manufacturers and they perform the clinical investigations on their behalf, always for market purpose.

The sponsor is empowered to temporarily stop or to terminate before the clinical investigations (Article 77).

Once the investigations are over, the sponsor must inform the concerned Member States within 15 days and he shall submit a report and summary of the performed activities that will be registered in an electronic system [32]. This electronic system is managed by the Member States and European Commission with the aim to generate a unique identification number for the clinical investigations, to report

the serious adverse event (SAE), any device deficiencies and to exchange the information related to the clinical investigations between them [23].
Another step, called Post-marketing data, of the clinical evaluation is dealt in the next paragraph of this thesis.

3.1.7 Post-Market surveillance, vigilance and market surveillance

The seventh chapter of the MDR aims to strengthen the vigilance and surveillance measures of devices in the post-market phase. Specifically, it defines the safety plan, following risks and incidents.
It is called "POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE" and it is divided into 3 sections [23]:

- Section 1 *'Post-market surveillance'* introduces and discusses the new phase of the analysis of the device after the market placing. It develops into 4 Articles from 83 to 86 and Annex III.
- Section 2 '*Vigilance'* includes from Article 87 to 92.
- Section 3 *'Market Surveillance'* from Article 93 to 100.

The first section, post-market surveillance, is a phase subsequent to market placing of the devices in which the manufacturers are obliged to collect, plan, apply and update a specific *Post-Market Surveillance plan (PMS)* for each type of medical device. The PMS plan includes two phases: *Pre-market phase* and *Post-market phase*, as is shown in Figure 25.

Figure 25: PMS plan process [33].

The manufacturers, in the pre-market phase, gather information on the design and manufacturing process and, in the second phase, highlight the safety, performances and risk-benefits of the devices that arise after-market placing.
Especially, the post-market phase is characterized by a *Post-Market clinical follow-up (PMCF)*. It consists of a collection of the post-marketing clinical data obtained within the clinical evaluation process (Figure 24).
In line to the Part-B of Annex XIV, the PMCF is defined as a continuous process that updates the clinical evaluation after the device is launched and it shall be addressed in the manufacturer's PMS plan [15,23]. The PMCF plan shall specify the methods and procedures for evaluating the clinical data, in order to confirm the safety and performance of the device, to identify risks, benefits and the side-effects [23]. These data are collected and are an integral part of the clinical evaluation.

The PMS is required for all the devices, executed in different ways, and should be part of the technical documentation (Annex III). The plan process is different based on the risk and the device classification. For the class I device, the manufacturers establish a report of *post-market surveillance report* (*PMSR*) that summarizes the results and conclusions of the surveillance analysis together with any preventive and corrective actions taken (Article 85) [23]. At the same time, for class IIa, IIb and III devices, the manufacturers prepare a *periodic safety update report (PSUR)* that sets out the conclusions of benefit-risks determination; results of PMCF and the volume of sales and the usage frequency of the device from the population (Article 86) [23].
Mainly, the manufacturers of class IIb and III update the PSUR at least annually and they submit the report via electronic system to the NBs, instead, for class IIa at least every two years [23].
Table 2 summarizes which report is required and at which stage for all the classes of devices, taking into account only the MDR.

Table 2: Post-Market reporting requirements [34].

Type	MDR or IVDR Classification	PMSR *or* PSUR?	How submitted?	Update frequency
MEDICAL DEVICE	**Class I**	PMSR	Only upon request	When necessary*
	Class IIa	PSUR	During Notified Body Conformity Assessment review	At minimum, every 2 years
	Class IIb (non-implantable)	PSUR	During Notified Body Conformity Assessment review	At minimum, every year
	Class IIb (implantable)	PSUR	Maybe via EUDAMED for Notified Body review	At minimum, every year
	Class III (all)	PSUR	Maybe via EUDAMED for Notified Body review	At minimum, every year

From table 2, it is possible to read “Maybe” via Eudamed because in Article 86, as mentioned above, the PSUR is sent via electronic system to the NBs but it is not specified by Eudamed. “When necessary” means, that for class I devices the NBs or Competent Authority may request the update at any time and not in a specific period [34].

The second section regards the vigilance of medical devices made available on the Union market. In this step, the manufacturer of the devices, points out, not later than 15 days, to the competent authorities, any serious incident involving devices and any field safety corrective action also corrective actions undertaken in a third country (Article 87) [23].

Once the incident has occurred, the manufacturer provides a risk assessment of the incident and field safety corrective action. He cooperates with the competent authorities including NBs during the investigations. If safety actions are taken, the manufacturer is required to notify the users with a field safety notice (Article 89) [23].

All these data, collected from the PSURs, report on serious incidents, the field safety notice and the information exchanged between competent authorities and Member States are uploaded on the electronic system of vigilance on order to exchange the information more easily (Article 92) [23]. This electronic information exchange system is inspired from the Eudravigilance, the European pharmacovigilance database launched in 2001 [28].

Chapter six ends with the market surveillance, third section. The new MDR strongly reinforces the obligations and the rights of the competent authorities in carrying out the necessary checks on medical devices. They verify the conformity characteristics and performances of the devices, including also a review of documentation. So, they draw up annual surveillance activity plan that will be evaluate by the Member States and share with the European Commission (Article 93) [23]. In case of unacceptable risk for health and safety of the patient, the competent authorities notify immediately the manufacturer with the aim of proceed with corrective actions (Article 95) [23].
Also, in that case, the Commission with the Member States prepares and manages an electronic system that contains the summaries of the results of surveillance, info about devices with high risk, info in relation to non- compliance, info about the preventive health protection activities (Article 100) [23].

3.1.8 Cooperation between Member States, medical device coordinator group, EU reference laboratories and device registers

The eighth chapter of the MDR, called "COOPERATION BETWEEN MEMBER STATES, MEDICAL DEVICE COORDINATOR GROUP, EU REFERENCE LABORATORIES AND DEVICE REGISTERS', delineates the key figures of the new Regulation. It includes 8 Articles from 101 to 108.

The MDR designs a real teamwork between three main figures:

- Competent Authorities.
- European Commission.
- Medical device coordination group (MDCG).

These figures, previously mentioned, are thus delineate competent authority is designed by the Member States and is called to carry out their tasks thorough knowledge and resources provide (Article 101). During the competent authority medical device meeting (CAMD), organized by the European Union, the General

Directorate of the Medical Devices and Pharmaceutical Service participates, for Italy, as competent authority [35].

In turn, the competent authority works closely with the Commission, which deals of the exchange of information, at international level, in the field of medical devices (Article 102) [23].

Each Member State appoints an experts' panel in the field of medical device, for three-year term which may be renewed, with the purpose to design *a medical device coordination group (MDCG)* (Article 103) [23]. MDCG tasks are disparate and are listed in Article 105 [23]. Some of these concern the evaluation of the safety requirements, the surveillance of the NBs, elaboration of medical device directives and so on.

The Commission together with the MDCG can design expert panels and expert laboratories in order to perform clinical and scientific opinions and advice (Article 106) [23]. Just the MDCG that, in March 2020, proposed a postponement, in May 2021, of the Regulation due to the exceptional circumstances associated with the Covid-19 pandemic.

3.1.9 Data protection, penalties and final provisions

The last two chapters "CONFIDENTIALITY, DATA PROTECTION, FUNDING AND PENALTIES" and "FINAL PROVISIONS" include the final articles until 123 Article.

The two last chapters define the final acts of the Regulation. One of the aspects is the *'Confidentiality'*, according to which all figures involved in this regulation respect the confidentiality of the information and data obtained in the performance of their duties (95/46/EC Directive) [23].

The penalties, applied in case of infringement of the provisions of this Regulation, are defined by the Member States who notified to the Commission (Article 113) [23].

Definitively, the MDR, according to the Article 123, was to be applied on May 26, 2020 but due to the Covid-19 pandemic, it is translated on May 26,

2021.Before the definitive transit of the Regulation, transitional provisions have been enacted (Article 120), according to which, for example, certificates issued by NBs, in accordance with Directives 90/385/EEC and 93/42/EEC prior to 25 May 2017, shall remain valid until the end of the period indicated on the certificate, except for certificates issued in accordance with Annex 4 to Directive 90/385/EEC or Annex IV to Directive 93/42/EEC which shall become void at the latest on 27 May 2022, or, by way of derogation from Directives 90/385/EEC and 93/42/EEC, devices which comply with this Regulation may be placed on the market prior to 26 May 2020 [23].

Another transition dates and applications of articles are listed in Article 123 [23].

Anyway, by 27 May 2027, the Commission shall assess the application of this Regulation and produce an evaluation report on the progress achieved.

3.2 MDR and Covid-19

3.2.1 Background

From March 12, 2020, date established by World Health Organization (WHO), the word is crossed by the outbreak of Covid-19 pandemic. Covid-19 is defined as a virus, discovered in China at the end of 2019 and in few months arrived across the continent, and up to now it is considered one of greatest challenges to which the human is subjected.

Nowadays, December 2020, few solutions to fight this virus, a vaccine incoming but still many troubles that the world health has to struggle.

Covid-19 virus, known as Coronavirus, is transmitted between the humans via small airborne droplets emitted by the infected people during the sneezing or talking [36]. So, wearing a personal protective equipment (PPE) or medical device, disinfecting the hands, surfaces and objects are the only actions to protect themselves.

In this context that, the medicine and the technology have tried to assist and to protect the patient’s health in the best possible way.

A wide array of medical devices is used, belonging to several risk classes but all characterized by a certification path before their placing on the market.
The wide demand of precise medical devices, such as face masks, gloves, intensive care equipment, has led to a tremendous burden on the medical device industry. The large devices contribution all over the world caused delays and shifts of some articles of the new MDR.

3.2.2 MDR implementation update

As previously mentioned, the pandemic brings a big request of medical devices by the health facilities and population so much that the manufacturing industries have forced to accelerate and jump some steps of the new Regulation in order to guarantee, as soon as possible, the useful means.
The European Commission was nominated to provide some scenarios in which the products could be placed on the market even if all the standard conformity assessment procedures had not been concluded.
This situation involved placing on the market of some medical devices without the CE mark as long as they ensure an adequate level of safety and health for the humans, in accordance with the essential requirements set in the Directive 93/42/EEC or new Regulation 2017/745.

Going deeply in the MDR, Article 59 *'Derogation from the conformity assessment procedures'* was immediately applied in order to reduce the duration of conformity procedures for the device with the intention to fight the virus and place speedily the devices on the market. This fast action was decided by the Legislative Decree of March 17, 2020, in which, in order to compensate the lack of medical devices, like face masks, it was assessed to trade devices without CE mark, until the end of emergency state.
According to Article 59, any competent authority may authorise, on a duly justified request, the placing on the market or putting into service within the territory of the Member State concerned, of a specific device for which the

procedures have not been carried out [23]. So, it is possible to empower the trading medical devices without CE mark for health public.

Other factors are reviewed by the European Commission with the aim to place the useful devices on the market as fast as possible. Some of them are the availability of device substitutes in the market, compliance with harmonized standards and essential requirements, results of reports or tests performed by the NBs and market surveillance [36].

Another delay involves in the nomination of the expert panels to compute clinical and scientific updates. All the devices requiring a Clinical Evaluation to reach the market under the MDR will be translated until May 26, 2021.

A review of the Chapter four on the NBs figure is performed. Many NBs are still going through the MDR designation and those who obtained the designation in 2019 will need to be re-designed in 2022 [36].

In addition, many industries of medical devices renewed their MDD and AIMD early, going to push their MDR transition dates to 2024 [36].

Postponing of the PSUR, periodic safety update report Article 86, to set out the conclusions of benefit-risks determination for class IIa, IIb and III devices. It will be submitted by the manufacturers to the NBs starting in May 2022 [36].

The last significant delay regards Eudamed database, mainstay of the new MDR. It will be operative only when the entire system and the different modules will reach their functionality. Currently, some pre-modules are available for the manufacturers and module for the economic operators should be ready at the beginning of 2021.

This series of MDR delays represent a good opportunity for the companies to improve the QMS, empowering and understanding the new figures and responsibilities.

3.2.3 Medical devices in the context of Covid-19

The medical devices used, at present, to fight Covid-19 pandemic are disparate as the many industries that, with a wide demand of devices, have operated to fight the virus.

The medical devices are subdivided in different classes based on the level of the risk, as usual:

- Class I, sterile and/or non-sterile with measuring function, Class IIa, IIb and Class III under Annex IX of MDD [37].
- Class I, Is, Ir, Class IIb, Class IIa and Class III under Annex VIII of MDR [37].
- Classification for in vitro diagnostic medical devices.

They are based on the type of the class and the route of the conformity assessment procedures is performed with or without the presence of NBs. Focusing only on the new MDR, the manufacturers should pay attention to the Article 52 *'Conformity assessment procedures'* and Annex IX, X, XI Part A and XI Part B.

A list of NBs for the MDR is available on the European Commission database, differ from the NBs for the MDD.

For Class Is and Im medical devices, as indicated in the MDR, the manufacturer shall consult the NBs and he sends them an application.

The NB figure was reviewed in the Covid-19 context. Due to the lockdown period, they could not perform onsite audits due to the travel restrictions, replacing by temporary extraordinary measures that consist in a new application to test the conformity. These guidelines applied to the relevant medical devices include in a document called '*Guidance on temporary extraordinary measures related to medical device notified body audits during COVID-19 quarantine orders and travel restrictions'*, issued by the MDCG and European Commission in April 2020 [36].

These new specifications are likely to have an impact on the minimum time and on the procedure to complete the certification assessment.

The trend of the time needed to complete a conformity assessment procedure for Class Is or Im is shown in Figure 26 [37].

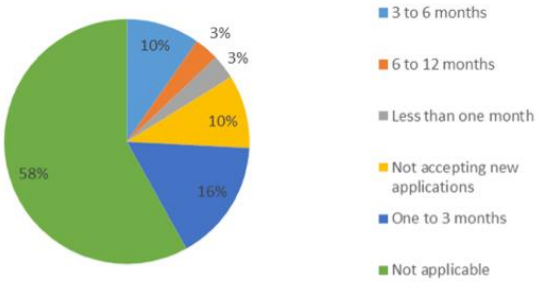


Figure 26: New application for conformity assessment of a device of Class Is or Im considered essential for Covid-19 under Annex IX or IX-part A [37].

It is possible to notice in Figure 26 that, 10% of the NBs do not accept the new application procedure and in 58% of the cases are not applicable.
Different are the times for Class IIa and Class IIb medical devices (Figure 27, Figure 28).

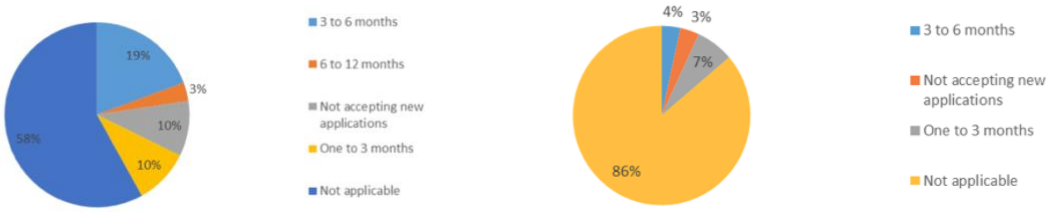


Figure 27: New application for conformity assessment of a device of Class IIa considered essential for Covid-19 under Annex IX-part B of MDR (Right); Annex IX or IX-Part A (Left) of MDR [37].

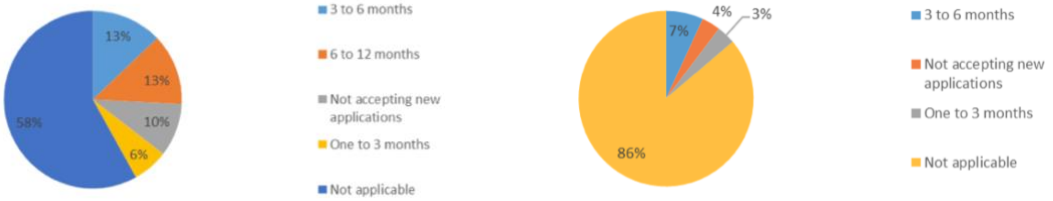


Figure 28: New application for conformity assessment of a device of Class IIb considered essential for Covid-19 under Annex X and X-part B of MDR (Right); Annex IX or IX-Part A (Left) of MDR [37].

The graphs, shown in Figure 26, 27 and 28, refers to the time needed for the conformity procedure, based on the device, for the new client who decided to trade the useful medical devices.

In accordance with the European Commission and WHO, the relevant medical devices subjected to a priority procedure in the context of Covid-19 are [36]:

- Monitoring equipment.
- Oxygen therapy equipment and accessories.
- Airway management and Intubation.
- Mechanical and Non-invasive ventilation equipment and accessories.
- ICU equipment and accessories.
- Imaging equipment and accessories.
- PPE.

All the Covid-19 essential devices, declared by the European Commission, are listed in European Website [1].

The next sub paragraph deals with one of the most used medical devices during the Covid-19 pandemic.

3.2.3.1 Focus on the face masks

Among the most requested and discussed medical devices, in the context of Covid-19, there are the face masks.

A *medical face mask* is a medical device and not PPE used to cover the mouth and the nose providing a barrier to minimize the direct transmission of infective agents between staff and patient as shown in Figure 29 [39]. It is constituted by a filter layer that is placed between textile layers and capable of not breaking or tearing during the use.

[1] European website: https://ec.europa.eu/info/sites/info/files/list-covid-19-essential-medical-devices_en.pdf, visited on December 2020

Figure 29: An example of a medical face mask [39].

During the first moths of the pandemic, the face masks have appeared unavailable and with a high price for the entire population. The availability was guarantee strictly to the healthcare professionals. For this reason, several has chosen to devote themselves to the production of face masks.

In Italy, the manufacturers must draw to the 'Istituto Superiore di Sanità (ISS)' an auto-certification in which the technical features, regarding the safety, of the face masks are explained. After three days of receipt of the documentation, ISS decide to approve or not the face masks produced [40]. All the available documents, including auto certification file, are available on the ISS website.

If the ISS declares that the features, submitted by the manufactures are not enough, the initial procedure or the impost of medical devices will not be granted.

The face masks are distinguished in distinct types and in different classification classes.

The class to which face masks belong, according to 93/42/EEC and MDR, is Class I and, principally, they observe the *Rule 1* of Annex VIII of MDR that analyses the non-invasive devices, i.e., devices that do not penetrate inside the body of the patient [23,38]. Specially, it is possible to distinguish in:

- *Class I-non-sterile*: Face masks disposable, after a period of time stops to work, they must have affixed the CE mark, obtained with only a self-assessment conformity procedure, submitted by the manufacturer, without the intervention of NBs [38] and with information of the manufacturer on the product. Hence, these face masks have the conventional CE mark without the series of numbers which indicate the NBs, like Figure 21.

- *Class Is*: Sterile face masks. They need the intervention of the NBs to assess the sterility process and validation of documentation.
- *Class Ir*: Reusable face masks. Also in this case the conformity assessment procedure is controlled by the NBs.

In addition to the classification in line with the new Regulation, a further distinction is made on the bacterial filtration efficiency (BFE) based on the harmonised European standard EN 146638 of 2019, in which the face masks are subdivided in Type I, II or IIR (splash resistance). Type I face masks are used only for patients and other persons in epidemic or pandemic situations (Figure 30) [38]. This face mask guarantees the non-diffusion of the human's infectious agents, but it does not protect to the external agents. The latter protection is possible wearing the *filtering facepiece particles (*FFP). The FFP are subdivided into three classes FFP1, FFP2 and FFP3, based on their filtering efficiency, and are not classified as medical devices by as dispositive individual protection (DPI), as shown in Figure 30.

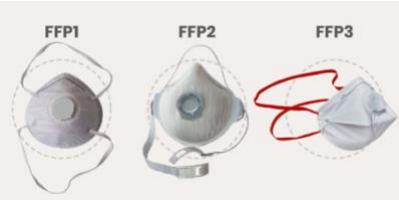


Figure 30: Examples of FPP masks [40].

Wearing the valve improves the breathing if the face mask is worn for a long time. The FFPs can be submitted or not to the judgement of the NBs but subjected to the conformity assessment procedure in line with the DPI regulation.
Last types of face masks existent on the market are the non-chirurgical face masks, not certificated for health use but just for aesthetic use (Figure 31).

Figure 31: Example of no-medical face mask [41].

It is important that all face masks bring on the label, the information according to the law, the intended use, belonging class and service life.

Placing a medical device on the market needs a precise condition: the CE mark affixed on the device and the EU declaration of conformity, in MDR, issued by the manufacturer [38].

In the Covid-19 context, where the demand for specific medical devices is exponential, the assessment procedures ensure a short-term supply but always guarantee an adequate level of safety and performance requirements. Specifically, Article 59 of MDR allows specific derogations from some requirements, carried out by the competent authorities of the Member State. These latter evaluates the available technical documentation to find evidence that the essential safety is respected [38].

Furthermore, has been drafted by the Commission Recommendation 2020/403 of 13 March 2020, based on the conformity assessment and on market surveillance, to allow more flexibility in placing certain medical devices on the EU market and to improve the availability of such products in this health emergency [38].

The industries that have decided to produce and market the face masks under its own name must assume the legal obligations and they need to fulfil the all the requirements of the MDD or the MDR.

For each class of classification, the route for the certification is different.

For Class I non-sterile face masks is required EU declaration of conformity to the Article 19 after drawing up the technical documentation set out in Annexes II and III of the MDR [38].

For Class I sterile face masks the procedure is the same of Class I non-sterile but with the presence of NBs according to the Chapter I and III of Annex IX or part A of Annex XI of MDR [38].

Nowadays finding a mask on the market is no longer a problem. There are different types and colours that you can find in various stores with a low price. This has been

possible thanks to the coordination between the industries, Member State, NBs and health institutions that, day by day, they tried to fight the problems.

Chapter 4

93/42/EEC AND 90/385/EEC VS MDR: MAIN CHANGES AND CHALLENGES

This last chapter aims to review some features of the Directives and the Regulation highlighting the changes and innovations that the new MDR brings in the European medical devices field.

4.1 93/42/EEC and 90/385/EEC vs MDR

The European medical devices world from 1993 has been headed by the actual, not for long, 93/42/EEC Directive known as MDD. It controls all types of devices except the active implantable medical devices, governed by the 90/385/EEC Directive.

The MDD is the reference guideline for the manufacturers, enterprises and industries to produce and to market a medical device until 2017, when the European Commission decided to redesign a new robust and transparent framework for medical devices called MDR.

There is no continuity between MDD and MDR. These are two different types of Legislation.

A first evident discrepancy is the type of the two laws. MDD and AIMDD are Directives and as such as they set a goal in all the European countries but do not define the lines to proceed, in terms of form and means. The parliaments can

implement additional requirements without changing or reducing the ones already expose [42].

Contrarily, MDR is a Regulation. It must be applied in all its elements within the European Union and it is supranational law within a given time [42]. It is not subjected to the approval of any national parliaments and all the figures, citated in it, must follow the articles and rules of its.

A second distinction is based on the entire structure: MDD and AIMDD are shorter and less complex then the MDR. The MDD is composed by 23 Articles and XII Annexes and AIMDD is only constituted by 17 Articles and 8 Annexes.

Completely different is the MDR. The new Regulation starts from some of the existing articles in MDD and AIMDD and it enlarges and modifies some existing concepts. The new guidelines include 123 Articles and XVII Annexes. The various articles are clustered in Chapters based on a defined topic.

The points are summarized in Table 3.

Table 3: Summary table of the structure between MDD and MDR.

	MDD	MDR
Type of Legislation	Directive	Regulation
Structure	•60 Pages •23 Articles •XII Annexes	•369 Pages •123 Articles •XVII Annexes

With this wide structure, MDR redesigns the entire production and marketing process of medical devices.

In Annexes III and IV of the thesis concordance tables based on the Articles and Annexes between the Directives and Regulation are shown.

4.2 Changes of MDR

The new Regulation introduces new ideas and changes the approach to the production and marketing. MDR is considered to be a milestone for the product safety and product quality of medical devices [31]. It was born only to improve the benefit of the patient.

All the changes and challenges achieved are presented in the next sub-paragraphs.

4.2.1 Product scope and definitions expansion

Starting from the beginning of the Regulation, the first change lies in the first Chapter “SCOPE AND DEFINITIONS”. This section is completely reviewed and amplified, according to the scope and definitions.

For what concern the scope (Article 1), the MDR is extended to the groups of products without an intended medical purpose listed in Annex XVI [23]. According to this Annex, the no-intended medical purpose group includes contact lenses, products intended to be totally or partially introduced into the human body to modify the anatomy or to fix body parts, substances for dermal or mucous membrane filling, equipment to reduce and remove the adipose tissue, high intensity electromagnetic radiation and brain stimulation equipment and reprocessed disposable medical devices [23]. Moreover, the scopes of no-application of the Regulation are mentioned.

As for regards the definitions (Article 2), 71 definitions are written in the MDR versus 9 definitions in MDD. These terms are the result of the combination of the existing definitions in the MDD and AIMDD in addition to the new ones. Among the news, there is the expansion of the medical device definition and the introduction of new figures. Products for cleaning, disinfection or sterilization and devices for the control or support of the conceptions, in MDR, are classified as medical devices.

4.2.2 Introduction of Common Specifications

Referring to the Chapter 1, MDR publishes the Common Specifications (CS) when the harmonized standards are not enough and are seen as State of Art [30]. These CS, adopted by the EU Commission, concern the GSPR set out in Annex I,

the technical documentations set out in Annexes II and III, the clinical evaluation and post-market clinical follow-up set out in Annex XIV or the requirements regarding clinical investigation set out in Annex XV [23].

4.2.3 Role of the economic operators

The second Chapter of the MDR outlines the role and the tasks of four main figures called economic operators, not present in MDD.
These figures are more consciously involved in the new Regulation. These characters are the manufacturer, authorized representative, importer and distributor implicated in the chain of production and marketing of the medical devices (Figure 32).

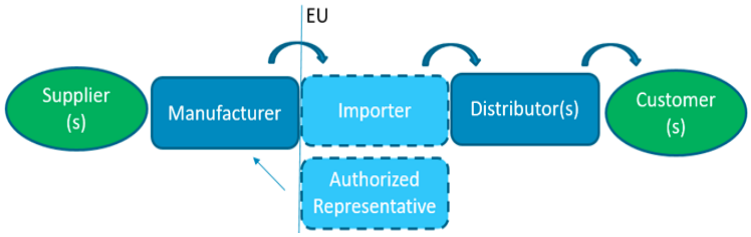


Figure 32: Economic Operators in the supply chain of the MDR [43].

Under MDR, each kind of personality has a precise and defined obligations to be respected, explained step by step in Articles 10, 11, 13 and 14, as mentioned in paragraph 3.1.2 of this thesis.
The chain starts with the figure of the **supplier**, selected by the manufacturer that provides for the realization of the medical device, and finishes with the **customer** (green circles in Figure 32). The process continues with the figures of **manufacturers** and **distributors**, defined in EU (blue circles in Figure 32) and with the **importer** and **authorized representative** named in the case of no-EU manufacturer (dashed light blue circles in Figure 32).
The manufacturer is called up to perform more specific assignments, like the PMCF and drafting of technical documentations, respect to the manufacturer in the MDD.

The authorized representative is introduced by the MDR in the case of non-EU manufacturer.
This new framework, only available in the MDR, leads to the CE conformity procedures, similarly to the MDD.

4.2.4 Identification of "qualified person"

Sticking to the second Chapter of MDR, a *qualified person* is introduced.
Article 15 launches a figure, within the organization of the manufactures, who is responsible for all the aspects regarding the compliance with the requirements of the new MDR.
The selection of this person is strictly accurate and reviewed by the NBs to ensure knowledge and skills.
His duties are explained in 3.1.2 paragraph.

4.2.5 Label content changes

New requirements of labelling are defined in the MDR. The information on the label are listed in the Annex I.
Specifically, the label includes [44]:

- Name or trade name of the device.
- Manufacturer date.
- Indication that the device is a medical device (MD).
- Warnings and precautions that need to be brought to the immediate attention of the user.
- Web address.
- Explicit requirements for sterile barrier labelling (identification the sterile barrier, declaration of the sterile condition, sterilization method, manufacture date, expiration date, directive to check the information of use (IFU) if package is damaged).
- Absorbed materials with the relative quantitative info on the main constituents.

These new points, compared with the MDD, are described in Figure 33

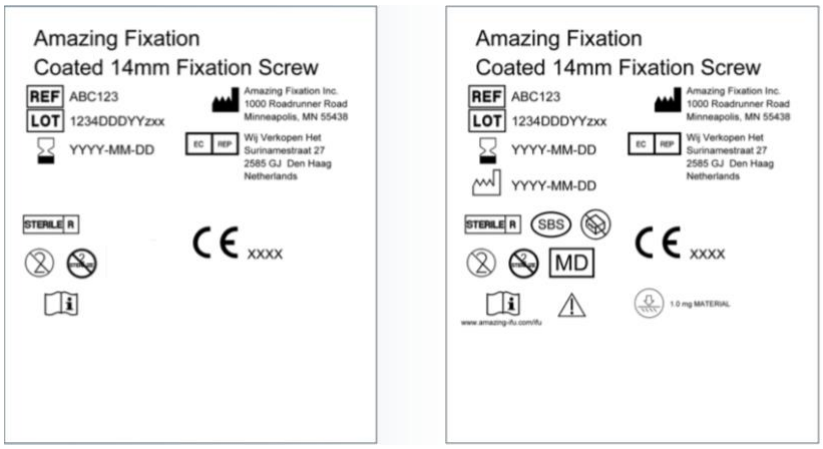


Figure 33: Label comparison between MDR (Right) and MDD (Left) [44].

4.2.6 Introduction of the patient implant card

MDR introduces an implant card. It is provided by the manufacturer who manages only the implantable devices. On this card, supplied to the patient together with the device, some features are affixed [23,44]:

- Device name.
- Serial number.
- UDI.
- Device model.
- Manufacturer name, address and website.

These features are shown in Figure 34.

Figure 34: Example of a patient implant card [44].

In addition to the card, the manufacturer provides any warnings, precautions or measures to be taken by the patient, info about the expected lifetime of the device and info to ensure safe use of the device (Article 18) [23].

In future the electronic version of the card will be recorded in clinics and hospitals.

4.2.7 Transparency and traceability of medical devices

The new Regulation deals with the problem of the lack of transparency and traceability of medical devices, existing in MDD.
The aim of the MDR is to provide more transparency to the traceability of the devices starting from the manufacturer to arrive to the patient or final user.
The traceability chain is composed by wide cooperation between the manufacturers, distributors and importers who are able to identify to whom they have supplied and who provided them the medical devices. The chain works thanks to new attributes, includes:

- Medical device nomenclature to assign an international and free name to the device, available to the manufactures and other legal or natural persons (Article 26) [23].
- Introduction of a European database on medical devices called Eudamed. It includes seven modules, controlled by an electronic system, by which it is possible to freely access in order to visualize the life cycle of the device (Figure 19) (Article 33) [23].
- UDI system to ensure the identification and traceability of the medical devices. Each type of device is constituted by an UDI code, assigned by the manufacturer, divided in UDI-PI and UDI-DI, as shown in Figures 17 and 18 (Article 27) [23]. All these codes recognize the device in a unique and global manner, are recorded UDI database (Article 28) in Eudamed and are available to know information about the device, whenever the companies want.
- Electronic system for registration of economic operators to identify the person (Article 30) [23].

- Use of an implant card to accompany the implantable devices with different info about the device (Figure 35).

4.2.8 The strengthened role of the Notified Bodies

The role of the NB is to evaluate the conformity assessment procedure of a medical device. The novelties carried by MDR lie in the tightening of their tasks, due to negative episodes occur under the MDD. They have a very important role in the pre-marking phase.
Designed by the European Commission with a specific identification number, the NBs are publicly accessible in an electronic database called NANDO.
The enhancement provides for:

- Severe requirements to be met based on independence, impartiality, confidentiality and liability.
- Accurate quality management system.
- New designation and notification procedures through joint evaluation between experts of Member States and Commissions.
- More detailed certifications of all the types of medical devices in pre- and post-market phases.
- Introduction of unannounced on-site audits and product testing at the manufacturer's premises.
- Installation of the scrutiny procedure for class IIb and III devices.

Ongoing training, knowledge, experience and objectiveness are the key words and should be the features of the NBs under the MDR.

4.2.9 Reclassification of medical devices

The classification of medical devices has been widely discussed in the previous chapters and this paragraph summarizes the changes and news of the MDR with to the MDD.

The standard classification and the risk assessment of the MDD based on four classes are still maintained with an implementation of 4 new rules and a further subdivision of the Class I medical devices in sterile, reusable and measurable indicated with Is, Ir and Im.

The four additional rules of the MDR compared with the MDD are shown in Figure 35.

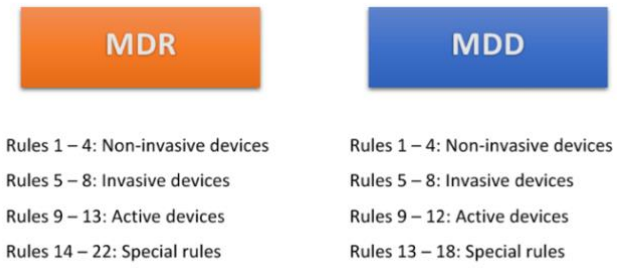


Figure 35: Rules comparison between MDR and MDD [45].

Particular attention should be paid on Rule 11, concerning the software, of the MDR differ from MDD. The Regulation introduces a classification of the softwares useful in the diagnosis or therapeutic purpose, dividing in I, II or III. An example of the software classification, denoted as medical device in MDR, is shown in Figure 36.

Another change regards the Class III devices. Some products will be classified in Class III from 2020 onwards, especially the products used in the heart or in the central circulatory system [31].

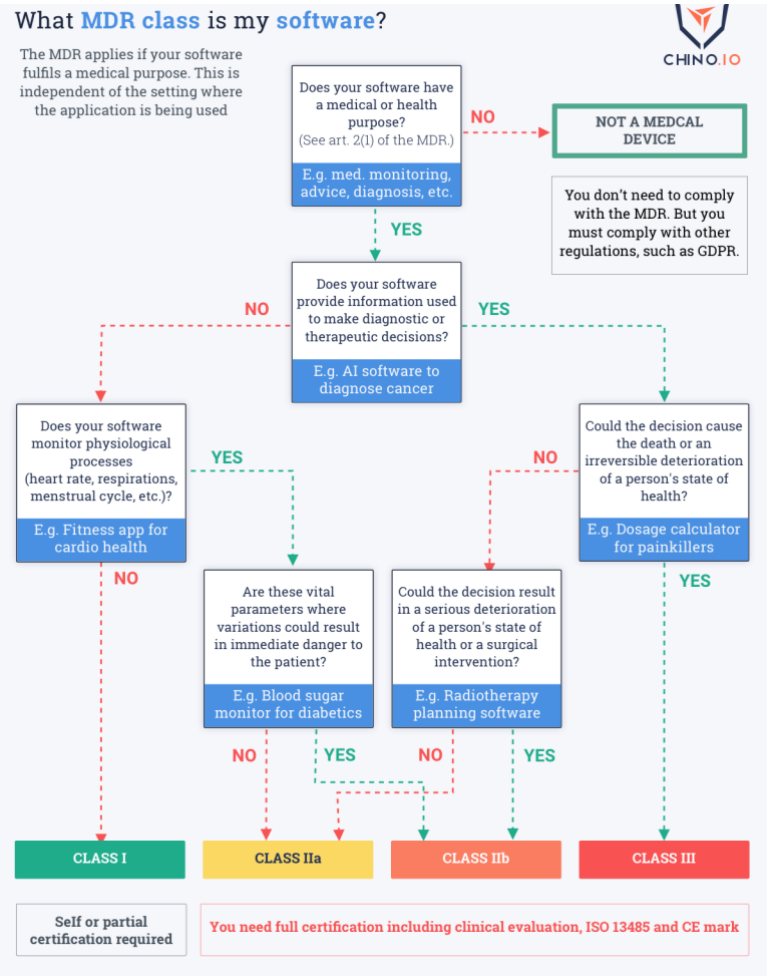


Figure 36: Software classification under MDR [46].

4.2.10 Strict technical documentation

Under MDR, the manufacturers are committed to draft a detailed technical documentation according to Annex II. They have to collect strictly info about the device description and specifications, design and manufacturing information, general safety and performance requirements, benefit-risk analysis and risk management and product verification and validation.

A furthermore technical documentation regards the info collected in the post-market phase (Annex III).

MDR provides a clear view of the different points that the manufacturer has to follow compared to the unstructured documentation given by the MDD.

4.2.11 Founding of Medical device coordination group (MDCG)

In MDR a medical device coordination group (MDCG) is established.
Group members are appointed by each Member State on the base of their competence and experience in the field of medical devices. They shall represent the competent authorities of the Member States and their name shall be public by the Commission [23].
As previously mentioned in Chapter 3 of this thesis, Articles 103 and 105 define the role and the tasks of the group. Some of their duties regard the contribution to the assessment of the NBs, the contribution to the continuous monitoring of technical progress and assessment of GSPR, support the Member State in the vigilance and market surveillance and advisement the Commission.

4.2.12 More rigorous clinical evaluation

With the entry in force of the MDR, a more rigorous clinical evaluation will be performed, especially for the Class III devices that need a particular attention for their high-risk level.
Clinical evaluation in MDR is strictly based on the collection of more data in order to verify the safety and performance of medical devices compared to MDD.
In order to carry out these procedures, a new figure, established in MDR, called sponsor performs a series of clinical investigations for the manufacturers in a very rigorous way, submitting a report with all information.
Unlike MDD, the Regulation sets severe points to follow and listed in Annexes XIV and XV.

4.2.13 Rigorous post-market surveillance and vigilance

The MDR, in Chapter 7, strengthens, defines and makes distinguishable two actions: PMS and vigilance process.
The PMS plan with its 6 phases is one of the new features of the MDR. The aim is to monitor as much as possible the experience of the devices after the placing on the market, involving all the economic operators. The plan is required for each type of medical devices, but it is performed in different way based on the class of the device. In all the cases the manufacturer has to submit a periodic report (PSUR) or PMSR, as shown in Table 2.
The limited vigilance requirements of MDD, deemed insufficient, have led to the strengthening of the vigilance system. The MDR presents a more detailed and rigorous vigilance process, coupled with the use of an electronic system, in Eudamed, to report SAEs so as to have immediate cooperation between the institutions and to take corrective actions. The paragraph 3.1.7 deals with these topics in a more specific way.

4.3 Challenges for the future

The new Regulation promises to be a real revolution in the field of medical devices, respect to the Directives. It introduces a series of measures, from scope to a rigorous clinical evaluation that will impact on companies' activities.
According to the "Direttore Generale di Confindustria dispositivi medici", the new Regulation strengthens the medical device system but, at the same time, it brings weakness and challenges for the future.
Due to its broad structure, MDR appears to be complex and quite articulated as it redefines and establishes new obligations, roles and tasks to the figures who, under MDD, were not considered significantly and it sets out rigorous procedures for market placing, for CE conformity assessment, for pre- and post-market surveillance and for vigilance.

Thanks to these novelties life will be difficult for those operators who have worked less well so far.

In the same way, these strict measures will be a challenge for small or large companies that will have to bear high costs.

The various costs and criticalities include:

- "Qualified person" useful for proper management of the requirement who can be an employee or advisor.
- Need of adequate facilities to perform clinical investigations, especially for the small companies.
- Massive CE marking procedure and difficulty in keeping it.
- Rigorous post- market surveillance.
- Reclassification of devices and introduction of medical software as medical device.
- Few NBs members to perform the conformity assessment, mainly in this re classification of the devices. This means that small and medium-sized enterprises will move abroad to look for NBs.

These critical issues have emerged since the manufactures and the other institutions approached to the Regulation with a view to the new certifications, planned for May 2021.

The current pandemic context does not help the European Commission and Ministry of Healthy to solve the raised problems. For this reason, that the medical device sector is trying to propose to Brussels a further extension of MDR in 2022, defined rules for the clinical evaluation and more funding for the pre- and post-market phases in order to have the availability of medical devices on European market.

As any Regulation, given its great impact, there is a transitional period, a period in which the following may be placed on the market.

The dates, listed in Table 4, refer to the Article 120 of the MDR shifted by one year, 2021.

Table 4: Transitional provisions according to medical devices classification.

RISK CLASS	OBTAINING THE DECLARATION OF CONFORMITY	PLACING ON MARKET
Class I	Before May 26, 2021	Until May 26, 2024
Class IIa, IIb and III	Certification issued by NBs after May 25, 2017	Until May 2024
Devices according to Annex IV of MDD and Annex 4 of AIMDD	Certification are valid until May 27, 2022	

Table 4 shows that, the Class I devices that obtain the declaration of conformity before May 2021, may be placed on the market until May 2024.

Similarly, if Class IIa, IIb and III have the certificate of conformity issued by NBs after May 25, 2017, may be placed on the market until expiry date (max 5 years) but no later than 2024.

In any case, a medical device that, do not undergo significant changes, are valid until 2024 (Article 120).

For all class of devices, the post-market surveillance and vigilance system will come in force in May 26, 2021.

Anyway, in 2021-2024 period the European market will be characterize by medical devices certificated under MDD and MDR.

CONCLUSIONS

The purpose of this thesis was to describe in detail the main points of the new medical device Regulation that will come in force in May 2021 amending the two still valid Directives MDD and AIMDD. The entire work is articulated in four chapters in order to start from the definition of a medical device under MDD up to the problems that led the European Commission to issue the new Regulation 2017/745.

Initially, the general features of the medical device world have been analyzed then moving to the properties of the actual Directives and the Regulation to make a comparison between them and to understand what MDR upsets or maintains. All the collected information are the result of an accurate literature review based on the literature articles and on a direct consultation of the Directives and Regulation which allowed a clear and detailed reconstruction.

Two major features of the MDR are the traceability and the transparency of medical devices. Thanks to the UDI code affixed on the device and European database is possible to reconstruct and visualize the cycle life of the device. These two characteristics are considered two powerful actions for the manufactures to obtain information about the device and, in the same time, are useful to avoid the counterfeiting of the devices on the market.

An additional factor that stands out is the increase of safety and health for the patients and users. This feature is supported by a strict conformity assessment procedure carried out by the NBs, by a clinical evaluation data-rich and by a post-market surveillance to verify the effective functionality of the device.

Moreover, the economic operators' tasks are strengthened in the chain of production and marketing of the devices.

This new MDR redefines the medical device field, leading to some problems, positivity and challenges for the future that the companies have to fight to market

their products. Thanks to an interview conducted by the “Direttore di Confindustria dispositivi medici” who works closely with the medical device’s companies, real difficulties have emerged in the implementation of the Regulation. The lack of NBs, only one in Italy, IMQ, able to execute the conformity assessment, the necessity to have an appropriate area to perform the clinical evaluation, proper figures able to enforce compliance and the upgrade of some devices are problems that the companies, in this period, are facing.

This thesis was intended to be a kind of help to the medical devices companies in understanding the main features and changes of the MDR that, they will follow from this May in the hope of marketing a medical device in Europe with few problems as possible.

Annex I

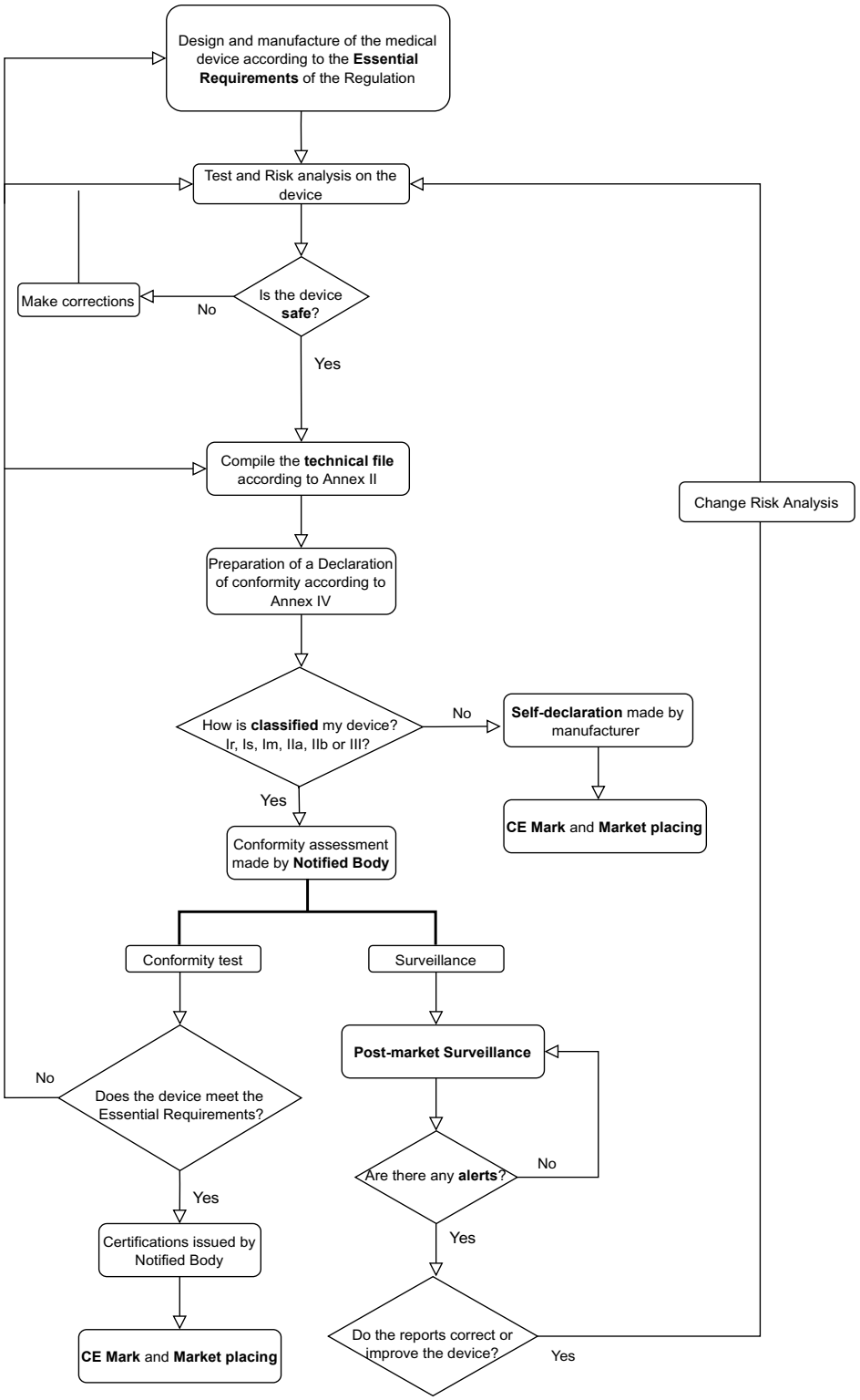
The 2020 top 30 global medical device companies [2]

	Company	Sales revenue US $ (billions)
1	Medtronic	$28.91B
2	Johnson & Johnson	$25.96B
3	Abbott	$19.95B
4	GE Healthcare	$19.94B
5	BD	$17.29B
6	Philips	$17.10B
7	Siemens Healthineers	$15.88B
8	Cardinal Health	$16.63B
9	Stryker	$14.88B
10	Baxter	$11.36B
11	Boston Scientific	$10.47B
12	EssilorLuxottica	$8.84B
13	B.Braun	$8.39B
14	Zimmer Biomet	$7.98B
15	3M Health Care	$7.43B
16	Alcon	$7.36B
17	Danaher	$6.56B
18	Fresenius	$6.37B
19	Olympus	$5.95B
20	Terum	$5.83B
21	Smith+Nephew	$5.13B
22	Intuitive Surgical	$4.48B
23	Edwards Lifesciences	$4.34B
24	Dentsply Sirona	$4.03B
25	Canon Medical	$4.02B
26	Hoya	$3.48B
27	Hologic	$3.36B
28	Hitachi	$3.25B
28	Varian Medical	$3.22B
30	Sonova	$3.05B

[2] Available online at: https://www.mpo-mag.com/issues/2020-07-01/view_top30/the-top-30-679842/ , visited on November 2020.

Annex II

Marketing path of a medical device



Annex III

Correlation table of the Articles between 93/42/EEC, 90/385/EEC Directives and the MDR 2017/745 [23]

Council Directive 90/385/EEC	Council Directive 93/42/EEC	Regulation 2017/745
Article 1	***Article 1*** *"Definitions, Scope"*	***Article 1*** *"Subject matter and scope" Chapter I "Scope and definitions"*
Article 1 (1)	Article 1, first paragraph (1)	Article 1 (1)
Article 1 (2)	Article 1 (2)	***Article 2*** *"Definitions"*
Article 1 (3)	Article 1 (3), first subparagraph	Article 1 (9) first paragraph
—	Article 1 (3) second paragraph	Article 1 (9) second paragraph
Article 1 (4) and (4a)	Article 1 (4)	Article 1 (8) first paragraph
Article 1 (5)	Article 1 (7)	Article 1 (11)
Article 1 (6)	Article 1 (5)	Article 1 (6)
—	Article 1 (6)	—
—	Article 1 (8)	Article 1 (13)
Article 2	***Article 2*** *"Placing on the market and putting into service"*	***Article 5*** *"Placing on the market and putting into service", Chapter II "making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement* (1)
Article 3	***Article 3*** *"Essential Requirements"*	Article 5 (2)
Article 3 (1)	Article 3 (1)	Article 5 (1)
Article 3 (2)	Article 3 (2)	Article 5 (2)
Article 4	***Article 4*** *" Free movement, devices intended for special purposes"*	***Article 24*** *"Free movement"*
Article 4 (1)	Article 4 (1)	Article 24
Article 4 (2)	Article 4 (2)	Article 21 (1) and (2)
Article 4 (3)	Article 4 (3)	Article 21 (3)
Article 4 (4)	Article 4 (4)	Article 10 (11)
Article 4 (5) (a)	Article 4 (5), first subparagraph	Article 20 (6)
Article 4 (5) (b)	Article 4 (5) second paragraph	—
Article 5 "…	***Article 5*** *"Reference to standards"*	***Article 8*** *"Use of harmonized standards"*
Article 5 (1)	Article 5 (1)	Article 8 (1)
Article 5 (2)	Article 5 (2)	Article 8 (2)

Article 6 (1)	Article 5 (3)	—
—	***Article 7*** *"Committee Medical Devices"*	***Article 114*** *"Committee procedure", Chapter X "Final provisions"*
Article 6 (2)	Article 7 (1)	Article 114
Article 7	***Article 8*** *"Safeguard clause"*	***Article 94*** *"Evaluation of devices suspected of presenting an unacceptable risk or other non-compliance"* ***Article 97*** *"Other non-compliance"*
—	***Article 9*** *"Classification"*	***Article 51*** *"Classification of devices", Chapter V "Classification and conformity assessment"*
Article 8	***Article 10*** *"Information on incidents occurring following placing of devices on the market"*	***Article 87*** *"Vigilance" and* ***Article 89*** *"Analysis of serious incidents and field safety corrective actions"*
Article 8 (1)	Article 10 (1)	Article 87 (1) and 89 (2)
Article 8 (2)	Article 10 (2)	Article 87 (10), Article 87 (11) first subparagraph
Article 8 (3)	Article 10 (3)	Article 89 (7)
Article 8 (4)	Article 10 (4)	***Article 91*** *"Implementing acts"*
Article 9	***Article 11*** *"Conformity assessment procedure"*	***Article 52*** *"Conformity assessment procedures"*
Article 9 (1)	Article 11 (1)	Article 52 (3)
—	Article 11 (2)	Article 52 (6)
—	Article 11 (3)	Article 52 (4) and (5)
—	Article 11 (4)	—
—	Article 11 (5)	Article 52 (7)
Article 9 (2)	Article 11 (6)	Article 52 (8)
Article 9 (3)	Article 11 (8)	Article 11 (3)
Article 9 (4)	Article 11 (12)	Article 52 (12)
Article 9 (5)	Article 11 (7)	—
Article 9 (6)	Article 11 (9)	Article 53 (1)
Article 9 (7)	Article 11 (10)	Article 53 (4)
Article 9 (8)	Article 11 (11)	Article 56 (2)
Article 9 (9)	Article 11 (13)	Article 59

Article 9 (10)	Article 11 (14)	Article 4 (5) and Article 122 third paragraph
—	***Article 12*** *"Particular procedure for systems and procedure packs and procedure for sterilisation"*	***Article 22*** *"Systems and procedure packs"*
—	Article 12, letter a (a)	***Article 17*** *"Single-use devices and their reprocessing"*
Article 9	***Article 13*** *"Decision with regard to classification and derogation clause"*	—
Article 9a (1)	Article 13 (1) (c)	—
—	Article 13 (1) (a)	Article 51 (3)(a) and Article 51 (6)
—	Article 13 (1) (b)	Article 51 (3)(b) and Article 51 (6)
Article 10	***Article 15*** *"Clinical Investigations"*	***Article 61*** *" Clinical evaluation "* to ***Article 82*** *" Requirements regarding other clinical investigations"*
Article 10	***Article 14*** *"Registration of persons responsible for placing devices on the market"*	Article 30
Article 10a (1,2,3)	Article 14 (1,2,3)	Articles 29(4), 30 and 31
Article 10a (2)	Article 14 (2)	Article 11 (1)
Article 10(b)	Article 14 (a)	***Articles 33*** *"European database on medical devices"* and ***Article 34*** *"Functionality of Eudamed"*
Article 10c	Article 14 (b)	***Article 98*** *"Preventive health protection measures"*
Article 11	***Article 16*** *"Notified Bodies"*	***Chapter IV*** *"Notified Bodies"*
Article 11 (1)	Article 16 (1)	Articles 42 and 43
Article 11 (2)	Article 16 (2)	Article 36
Article 11 (3)	Article 16 (3)	Article 46 (4)
Article 11 (4)	Article 16 (4)	—
Article 11 (5)	Article 16 (5)	Article 56 (5)
Article 11 (6)	Article 16 (6)	Article 56 (4)
Article 11 (7)	Article 16 (7)	Articles 38 (2) and 44 (2)
Article 12	***Article 17*** *"CE marking"*	***Article 20*** *"CE marking of conformity"*

Article 13	***Article 18*** *"Wrongly affixed CE marking"*	***Article 94*** *"Evaluation of devices suspected of presenting an unacceptable risk or other non-compliance"* ***Article 97*** *"Other non-compliance"*
Article 14	***Article 19*** *"Decision in respect of refusal or restriction"*	***Article 99*** *"Good administration practice"*
Article 15	***Article 20*** *"Confidentiality"*	***Article 109*** *"Confidentiality"*
Article 15a	*Article 20 (a)*	***Article 102*** *"Cooperation"*
Article 16	***Article 22*** *"Implementation, transitional provisions"*	—
Article 17	***Article 23***	—
—	***Article 21*** *"Repeal and amendment of Directives"*	—

Annex IV

Correlation table of the Annexes between 93/42/EEC, 90/385/EEC Directives and the Medical Device Regulation (UE) 2017/745 [23].

Topic of the Annexes	Council Directive 90/385/EEC	Council Directive 93/42/EEC	Regulation 2017/745
Essential Requirements	Annex I	Annex I	Annex I
Declaration of Conformity	Annex II Annex V Annex VI	Annex II Annex III Annex IV Annex V Annex VI Annex VII Annex VIII	Annex IV Annex IX Annex X Annex XI
Classification	–	Annex IX	Annex VIII
Clinical Evaluation	Annex VII	Annex X	Annex XIV Annex XV
Notified Bodies	Annex VIII	Annex XI	Annex VII Annex XII
CE Marking	Annex III Annex IV	Annex XII	Annex V
Technical Documentation	–	–	Annex II
Technical Documentation on post-market surveillance	–	–	Annex III
Information to be submitted upon the registration of devices and economic operators, UDI database	–	–	Annex VI
Performance evaluation, performance studies and post-market performance follow-up	–	–	Annex XIII
Correlation table	–	–	Annex XVII

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