MASTER IN BIOMEDECINE

Present and future developments regarding the regulatory framework for medical devices in Europe

GEGA, Keis

Award date:
2023

Awarding institution:
University of Namur

UNIVERSITÀ DEGLI STUDI DEL PIEMONTE

ORIENTALE "AMEDEO AVOGADRO"

DIPARTIMENTO DI SCIENZE DEL FARMACO

EMOTION

The European Master in Translational Cosmetic and Dermatological Sciences

Thesis

Present and future developments regarding medical devices and their regulatory framework in Europe.

Tutor

Prof. Jean - Pierre Gillet

Candidate

Keis Gega

Academic Year 2021-2023

Session September 2023

EMOTION

AN ERASMUS MUNDUS MASTER

UNIVERSITÀ DEGLI STUDI DEL PIEMONTE ORIENTALE
"AMEDEO AVOGADRO"

UNIVERSITÀ DEL PIEMONTE ORIENTALE

EMOTION

The European Master in Translational Cosmetic and Dermatological Sciences

and

UNIVERSITÉ DE NAMUR

UNIVERSITÉ DE NAMUR

Master en Sciences Biomédicales, Finalité Spécialisée en Recherche Clinique

Thesis

Present and future developments regarding medical devices and their regulatory framework in Europe.

Tutor

Prof. Jean - Pierre Gillet

Candidate

Keis Gega

Academic Year 2021-2023

Session September 2023

Declaration of Authenticity

I, Keis Gega, enrolled in the European Master in Translational Cosmetic and Dermatological Sciences at Dipartimento di Scienze del Farmaco (EMOTION), Università del Piemonte Orientale (UPO) and discussing the Thesis in September 2023 (extraordinary session)

declare that

- This thesis is my own original work, based on my personal study, experience and/or research.
- I have acknowledged all material and sources used in its preparation (*e.g.* books, articles, reports, lecture notes, and any other documents, including websites or personal communications).
- I am aware that false statements will be punished by law (art. 76 del D.P.R. 28.12.200 n.445).

Date___28.08.2023_____Signature_____ 

Disclaimer: The information presented in this master thesis does not reflect the official opinion of the European Commission.

Abstract: A general overview of the medical devices industry's trends and the related

regulatory framework in Europe.

Background: The medical device industry is essential for promoting and enhancing the overall quality of life and improving healthcare outcomes and is characterized by competitiveness and innovation. Medical devices have seen a major change in the healthcare sector during the last several decades. Considering the rapid growth of this industry and the latest developments in this regard, present and future considerations related to the field have been taken into account.

Aim: The purpose of this master thesis is to recognize the importance of medical devices; providing a mirror of the situation and its coverage in Europe, the history of how the medical device industry has started and evolved in the world and especially with the description of the current and future developments in the field, digital transformation, as well as a general overview regarding the legal framework for medical devices in Europe.

Methods: The master thesis is based on the literature review of the present legislation of medical devices in force in Europe and beyond on the latest developments related to the field. The sources of information mainly include the Regulation (EU) 2017/745 on medical devices; Regulation (EU) 2017/746 on in vitro diagnostic medical devices and guidance documents, as well as other materials published on the official websites of the European Commission, European Parliament, Statista and other official websites of national competent authorities and other institutions of European countries.

Results and conclusions: The Regulation (EU) 2017/745 and Regulation (EU) 2017/746 serve as the cornerstone of the EU regulatory framework for medical devices, enhancing patient safety and device performance for the benefit of patients/users and the general public. Initiatives undertaken at EU level and country level are considered important in order that all the patients will be able to benefit from the availability of safe and innovative medical devices in Europe. Present and future developments in the field are expected to transform the industry and the system in the upcoming years and we are eager to witness the revolutionization.

Introduction of the host organization:

I performed my traineeship at the European Commission - Directorate General Food and Health Safety (DG SANTE) - Unit D3. The European Commission is the EU institution responsible for the proposal of new policies and that monitors in a constant manner the implementation and the application of these policies.

The Commission is divided into Directorates-General (DGs), or policy departments, each of which is in charge of a certain area of policy. Each DG is organised in Units, according to the specific area.

Unit D3 is the Unit where I performed my traineeship and is specifically responsible for the development and implementation of the regulatory framework for medical devices with the goal of ensuring a high level of patient safety and health, as well as to boost the competitiveness of the industry.

Table of contents:

1. Introduction.....7

1.1. The value of medical devices 7

1.2. History of the medical devices legislation.....7

1.3. Changes presented by the new regulatory framework for medical devices 9

1.4. Transition from the directives to the new regulations 12

2. Materials and Methods 14

3. Results.....14

3.1. The regulations and other guidance documents.....14

3.2. Latest developments 18

3.3. Digital transformation……21

4. Discussion……..22

5. Acknoledments……...25

6. References:.....26

List of acronyms

1. MD - Medical Device
2. IVD - In vitro diagnostic medical device
3. MDCG - Medical Device Coordination Group
4. MDD - Medical Device Directive
5. MDR - Medical Devices Regulation
6. AIMDD - Active Implantable Medical Devices Directive
7. IVDD - In Vitro Diagnostic Medical Devices Directive
8. IVDR - In Vitro Diagnostic Medical Device Regulation
9. EU - European Union
10. EC- European Commission
11. EP - European Parliament
12. EUDAMED - EU database on medical devices
13. PIP - Poly Implant Prothèse
14. EPSCO - Employment, Social Policy, Health and Consumers Affairs Council
15. UDI - Unique Device Identifier
16. CIE - Clinical Investigation and Evaluation
17. NB - Notified Body
18. NBCG - Notified Body Coordination Group
19. NBO - Notified bodies oversight
20. MS - Market Surveillance
21. PMSV - Post-market surveillance and vigilance
22. B&C - Borderline and classification
23. CS - Common Specifications
24. PMCF - Post-market clinical follow up
25. PSUR - Periodic Safety Update Report
26. SRN - Single Registration Number
27. QMS - Quality Management System
28. EMDN - European Medical Device Nomenclature
29. OJEU - Official Journal of the European Union
30. ISO - International Organization for Standardization
31. AI - Artificial intelligence
32. VR - Virtual Reality
33. GPT - Generative Pre-trained Transformer
34. MEP - Member of the European Parliament
35. DiGA - Digitale Gesundheitsanwendungen (in German) - Digital Health Applications
36. SME - Small and Medium Enterprise
37. FAMHP - Federal Agency for Medicine and Health goods (FAMHP)
38. NIHDI - The National Institute for Health and Disability Insurance
39. BfArM - Bundesinstitut für Arzneimittel und Medizinprodukte (in German) - The Federal Institute for Drugs and Medical Devices

1. Introduction

1.1. The value of medical devices

The annual value of the medical devices market in Europe is expected to increase from 145.8 billion $ in 2021 to 204.5 billion $ in 2027, with an increase of 40.26 % during these 6 years. (1) These data combined with the fact that the market offers more than 500,000 types of medical devices, reflect the rapid growth of the medical device industry and predict the transformation of this industry in the future. (2, 28) The medical device industry is essential for promoting and enhancing the overall quality of life and improving healthcare outcomes. (18)

Article 2 of Regulation (EU) 2017/745 defines a ‘’medical device‘’ ‘’*any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*
— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
— providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means‘’. (19)

As they aid in the diagnosis, monitoring, and treatment of a wide range of medical conditions, medical devices are a crucial component of healthcare. Medical devices have seen a major change in the healthcare sector during the last years. They range from basic ones to sophisticated surgical robots and are essential in the management and prevention of chronic illnesses, too. Additionally, they can support patients in better health outcomes and lower healthcare costs by assisting them in managing their health conditions. (18) The pandemic-accelerated technological advancements has played a special role and has sped up the transition to digital and personalized medical treatment. (3)

1.2. History of the medical devices legislation

The legal framework for medical devices in EU as mentioned below was harmonized in the 1990s:

- The Council Directive 93/42/EEC on Medical Devices (MDD) (1993),
- Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990),
- Directive 98/79/EC of the European Parliament and of the Council on In Vitro Diagnostic Medical Devices (1998).

However, the history before the 1990s was different. The 1800s were a pivotal time in the

development of therapeutic and medical technologies, as well as medical devices. The stethoscope and electrocardiogram were among the innovations introduced to the market in the 19th century. On the other hand, the development of other medical devices, such as the insulin pumps, or the cardiac defibrillator exploded in the 20th century. The medical devices industry has its roots primarily in the 1930s and saw a rapid evolution following World War II thanks to the development of synthetic polymers and rising electrical and electronic technologies. Additionally, during the same time, a ‘’proliferation’’ of novel and ground-breaking devices was seen, particularly in the field of cardiovascular space. Without any regulations or control from the government regarding their safety or performance, medical devices were manufactured by small businesses or doctors and marketed directly to the general public. (21)

The directives were amended by several subsequent legal acts. The MDD, also known as Directive 93/42/EEC, is the Medical Device Directive. It functioned as the most significant regulatory document in Europe for more than two decades. It was first introduced in 1993 (and amended in 2007 by Directive 2007/47/EC). As all directives, also this one had to be transposed into national legislation by all European states. The MDD truly established the "essential requirements" to market medical devices in the European Union and also with the purpose of guaranteeing in this way the free movement of devices throughout Europe. (20)

In March 2010, the so-called ‘’PIP scandal’’ took place with the involvement of more than 400.000 women. Poly Implant Prothèse (PIP) was a French company, specialized in the manufacture and sale of silicone gel breast implants, founded in 1991. Following the large number of complaints from the users and the healthcare professionals, as well as serious adverse events from the use of these implants, the inspection of the French Health and Safety Agency (AFFSAPS) lead to the discovery of a fraud, as the manufacturer was using another gel (a cheaper one) instead of the medical grade gel NUSIL. As a result, the manufacturing site was shut down and the marketing of PIP implants was banned globally by the French Minister of Health. (5, 6)

In 2012, under the existing Medical Devices legal framework, among the actions taken on this regard, it was also launched an Action Plan for Immediate Actions. A Commission Staff Working Document was discussed by the Employment, Social Policy, Health and Consumers Affairs Council (EPSCO) on June 20, 2014. This document included a thorough examination of how the joint actions made by the European Commission and EU Member States within the parameters of the PIP Action Plan were implemented. Following the discussion, it was decided to move forward with a second set of actions addressing the issues that were deemed problematic in the Commission Staff Working Document. Among these measures were improvements to communication and transparency, notified bodies' operation and market surveillance. (7)

In order to address the above-mentioned issues and update the regulatory framework, the European Commission presented two regulation proposals in September 2012. Following the first readings by the European Parliament in April 2014, the Council decided upon its stance in October 2015. At the conclusion of the trilogue discussions on May 25, 2016, agreement was reached on both proposals. The Permanent Representatives Committee of the Council approved

this on the 15th of June and the ENVI Committee of Parliament did the same. In September, the Council came to a political consensus. (4)

1.3. Changes presented by the new regulatory framework for medical devices

A new regulatory framework was established and the three directives have been updated by the European Union taking into account advancements during the last two decades. The new regulations: Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices, were adopted in May 2017. The AIMDD and MDD were repealed and as well replaced by the Medical Device Regulation (also called MDR) - Regulation (EU) 2017/745 on May 26, 2021, after the EU revised the medical devices' regulatory framework. (8, 9)

The MDR improved the harmonisation of how those criteria are applied across Member States by strengthening the requirements on device safety and performance throughout their lifecycle. After a five-year transition period, the new In Vitro Diagnostic Medical Devices Regulation (also called IVDR) - Regulation 2017/746 replaces and repeals the IVDD on May 26, 2022. The two regulations set standards regarding the safety and performance of in vitro diagnostic medical devices and medical devices, while maintaining the level of protection of health for users and patients. The transition from the previous directives to the current regulations, reflected the reinforcement of some of the key elements of the directives, as well as included a number of very significant changes and improvements to the system (8, 9):

- **Increased transparency via a system for tracing devices based on a unique device identification (UDI) and an EU database on medical devices (EUDAMED) (8)**

As per article 33 of Regulation (EU) 2017/745, provisions related to the establishment, maintenance, and management of the European database on medical devices (referred to as "EUDAMED") are presented. EUDAMED is an IT system, an integral part of the implementation of the legal framework in force of the medical devices. The Commission implementing Regulation (EU) 2021/2078 of 26 November 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the European Database on Medical Devices (EUDAMED), includes specific procedures required for the creation and upkeep of EUDAMED. A public website and six related sections make up the structure of EUDAMED:

- *EUDAMED public*
- *Registration of actors (available since December 2020)*
- *Device registration/UDI (available since October 2021)*
- *Clinical Investigations and Performance Studies*
- *Notified Bodies and Certificates*
- *Market surveillance*
- *Post-market surveillance and vigilance*

The Unique Device Identifier (UDI), as defined in article 2 of Regulation (EU) 2017/745 and its

system as described in article 27 and Part B and C of Annex VI of the same Regulation must provide the identification and ease the traceability of devices (excluding devices used in research - investigational devices and custom-made devices). (19, 24)

- **Stricter prior control for high-risk devices with the involvement of EU expert panels. (8)**

According to article 106 of Regulation (EU) 2017/745, expert panels are chosen by the European Commission based on their current scientific, clinical, or technological knowledge in the relevant field, as well taking into account their geographic distribution, which will represent the variety of scientific and clinical expertise used throughout the Union. The manufacturer may consult an expert panel as described in Article 106 of Regulation (EU) 2017/745 before conducting clinical evaluation or/and investigation for all class **IIb** devices and class **III** devices, with the purpose of reviewing the intended clinical development strategy of the manufacturer and suggestions for clinical investigation. (19)

- **Strengthening of clinical investigation and evaluation (CIE) rules (8)**

Chapter VI of Regulation (EU) 2017/745 presents detailed information and provisions regarding the clinical evaluation, as well as requirements related to the clinical investigation in order to demonstrate the conformity of medical devices. Special requirements are foreseen for clinical investigation in minors, incapacitated subjects, emergency situations and pregnant/breastfeeding women. The procedure for the conduct and application of clinical investigations are also described in this chapter. Annex XV of the same Regulation provides general requirements, documentation for the clinical investigation (including the application form and clinical investigation plan, as well as investigator's brochure, and other information) and also other obligations of the sponsor. (19)

- **Stronger criteria for designation and procedures for oversight of notified bodies (NBs) (8)**

The concept of ''authority responsible for notified bodies'' is presented in the Chapter IV of Regulation (EU) 2017/745, as the responsible authority for the assessment, designation, monitoring and notification of conformity assessment bodies. Under the same chapter are introduced provisions regarding the requirements related to notified bodies and application procedure by conformity assessment bodies for designation, as well as the assessment, notification procedure, and monitoring of these notified bodies. (19)

Also, according to article 49 of the Regulation (EU) 2017/745, in the area of medical devices (including in vitro diagnostic medical devices), the Commission should make sure that proper coordination and cooperation amongst notified bodies is established and run in the form of a Notified Body Coordination Group (NBCG). The same article presents the requirements regarding an approximation related to the frequency of the meetings of this group (regularly, at

least once a year) and the notified bodies' participation (notified bodies in accordance with this Regulation must take part in the group's work). (19)

- **New classification system (risk) for in vitro diagnostic medical devices (IVDs) (8)**

According to article 47 of Regulation (EU) 2017/746, the intended use of the in vitro diagnostic medical devices and their associated risk shall be taken into consideration when categorizing them into classes A, B, C and D. The application of classification shall be in line with Annex VIII of Regulation (EU) 2017/746. MDCG 2020-16 REV.2 covers the classification of in vitro diagnostic medical devices (IVDs), as well as provides clarifications and information on the classification standards as set forth in Annex VIII of Regulation (EU) 2017/746. This document's main goal is to give health institutions, manufacturers and notified bodies (NB) advice on how to classify an IVD before making it available/placing it on the market/putting it into service. (19, 25)

- **Strengthening of the requirements related to post-market surveillance (PMS) for manufacturers and improving mechanisms of coordination between EU countries in the fields of vigilance as well as market surveillance (8)**

As an important part of the quality management system (QMS) of the manufacturer, the postmarket surveillance system - PMS (based on a post-market surveillance plan) for each medical device must be planned, documented, established, maintained, implemented, and of course updated in a way that is proportionate to the type and the risk class of the device. Provisions regarding the post-market surveillance report (devices part of class I), as well as periodic safety update report - PSUR (class III, IIa, and IIb devices) are also introduced in Section 1 of Chapter VII of Regulation (EU) 2017/745. Under the same chapter of the Regulation (EU) 2017/745, special provisions are also foreseen for reporting serious incidents as well as field safety corrective actions from manufacturers and market surveillance activities from national competent authorities. (19)

- **Inclusion of some aesthetic devices within the scope of the regulation on medical devices (Annex XVI) (8)**

Annex XVI of Regulation (EU) 2017/745 lists the products without an intended medical purpose, referred in article 1(2) of the above mentioned regulation. Rules for the application of the Regulation (EU) 2017/745 as concerns the reclassification of groups of specific products without an intended medical purpose are set forth in the Commission Implementing Regulation (EU) 2022/2347. Common specifications (CS) are established by Commission Implementing Regulation (EU) 2022/2346, as revised by Implementing Regulation (EU) 2023/1194, for the categories of products without an intended medical use that are mentioned in Annex XVI of the Regulation (EU) 2017/745. (21)

- **Introduction of an "implant card" for patients that contains details on medical devices that have been implanted (8)**

Provisions related to the information that must be supplied to the patient that have an implanted device are introduced in article 18 of Regulation (EU) 2017/745. (8)

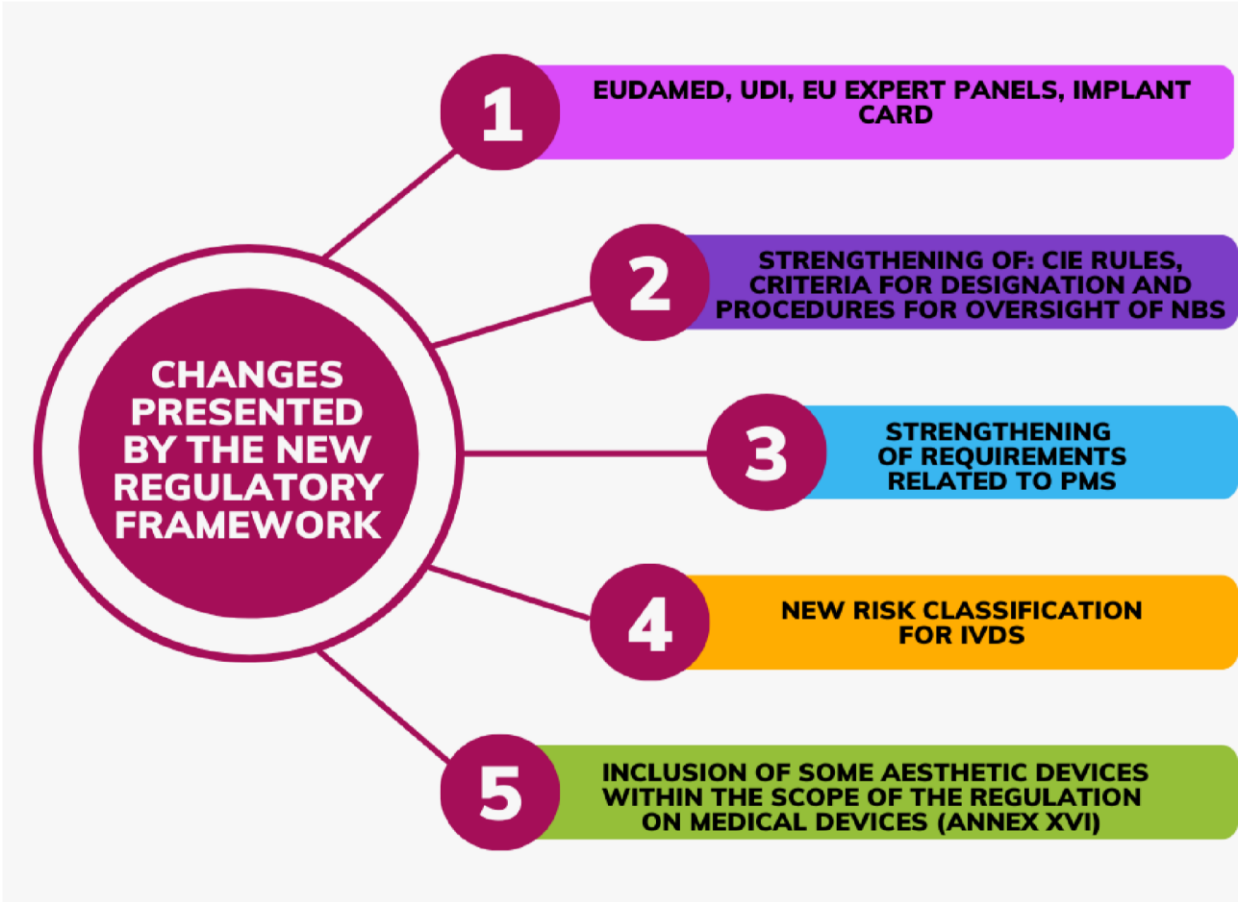

Fig. 1. Changes presented by the new regulatory framework for medical devices (made with Canvas)

1.4. Transition from the directives to the new regulations

The MDR or Regulation (EU) 2017/745 on medical devices was adopted in April 2017. It entered into force in 2017 (May), as amended (applicable from May 2021, because of a one year postponement by Regulation (EU) 2020/561, as caused by the COVID-19 pandemic). The end date of the transitional period (for devices that comply with the Directive 90/385/EEC or the Directive 93/42/EEC) and may be placed on the market/put into operation was maintained as 26 May 2024. (9)

The In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 was adopted in April 2017 and came into effect in May 2017 (applicable as of May 26, 2022). The transitional period that

was provided in Regulation (EU) 2017/746 was already extended (Regulation (EU) 2022/112). (9)

Notwithstanding the consistent expansion in the quantity of notified bodies designated as per Regulation (EU) 2017/745, their capacity and readiness was not sufficient to guarantee the conformity assessment of a majority number of devices that are covered by certificates issued by the Directive 90/385/EEC or the Directive 93/42/EEC (before May 2024). Another important aspect taken into consideration while monitoring the market in a constant manner, apart from the readiness of notified bodies, was also the proper readiness of other parties involved such as competent authorities, other economic operators (manufacturers etc). (10, 11, 28)

On a note from the General Secretariat of the Council to the Council of the European Union (published in December 2022), taking cue from the meeting of the EPSCO Council (Health) in December 2022, an update of the situation regarding the implementation of the Regulation (EU) 2017/745 was provided, considering all the concerns expressed by the health ministers of the European countries on this regard. Data from notified bodies regarding the applications from manufacturers and the certificates issued from the notified bodies under the Regulation (EU) 2017/745 and Regulation (EU) 2017/746, as well as under the Council Directives 90/385/EEC, 93/42/EEC and Directive 98/79/EC were also taken into account. (10, 11, 28)

Considering all these aspects, in order to mitigate the risk of shortages of medical devices in the European Union, the *Regulation (EU) 2023/607 of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746,* presented transitional provisions regarding the extension of the validity of certificates that were issued in accordance with the Directives 93/42/EEC and the Directive 90/385/EEC, and the extension of the transitional period for which devices are conform with the above mentioned Directives can be placed on the market lawfully. The length of the transitional period must depend on the risk class of the devices that are concerned (the period is longer for devices belonging to a lower risk class and shorter for devices belonging to a higher risk class). The ‘’sell-off’’ date is likewise removed from the MDR and IVD Regulations: Article 120(4) of MDR and Article 110(4) of IVDR. This cancellation enables devices marketed before or during the transitional period to be sold without a time constraint. (10, 11, 28)

According to Regulation (EU) 2023/607, the new dates of placing on the market/putting into service for the devices having a certificate (valid) issued in compliance with Directive 90/385/EEC or Directive 93/42/EEC are:

a. for all class III devices and class IIb implantable (with some exceptions presented in the Regulation (EU) 2023/607: December 31, 2027
b. Class IIb devices that aren't covered by point (a) above, class IIa and devices and class I devices that are put on the market in sterile condition or with a measurement function: 31 December 2028. (10, 11, 28)

The Q&A *on practical aspects related to the implementation of Regulation (EU) 2023/607 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices* was first issued in March

2023 and revised in July 2023. The purpose of this document (as explained in the beginning of the document itself) is to make it easier to apply Regulation (EU) 2023/607 of the European Parliament and of the Council of March 15, 2023, amending Regulations (EU) 2017/745 (MDR) and (EU) 2017/746 (IVDR) with regard to the transitional provisions for certain in vitro diagnostic medical devices and medical devices. Furthermore, on the 23rd of August, the European Commission published a Flowchart to help manufacturers and other key stakeholders determine whether a device qualifies for the longer transitional period specified in Article 120 of Regulation (EU) 2017/745 on medical devices (MDR), as revised by Regulation 2023/607. The flowchart ought to assist in defining the eligibility, timeframes and also the conditions for the placing on the market or implementation of specific devices as defined by Article 120 of Regulation (EU) 2017/745. (source: the Q&A and flowchart documents published in 2023)

2. Materials and Methods

This paper is based on the literature review of the present legislation of medical devices in force in Europe and beyond on the latest developments related to the field. It is mainly focused on the chronological order of the evolution of medical devices during the years and an overview of the legal framework of medical devices in Europe, including the most important changes that the current legal framework in Europe has introduced. The sources of information include the Regulation (EU) 2017/745 on medical devices, Regulation (EU) 2017/746 on in vitro diagnostic medical devices and guidance documents, as well as other materials, factsheets, infographics published by the European Commission, European Parliament, Statista and official websites of national competent authorities and other institutions of European countries.

Other websites and papers, as included in the References part of this master thesis were also consulted for certain elements that were considered important taking into account the subject of the thesis. The design primarily consists of the information that is publicly available and publications, databases produced and maintained by European institutions such as the European Commission and the European Parliament, as well as the other national competent authorities and institutions of EU countries. Specific papers were consulted especially as regards the new technologies and latest developments on the field of medical devices and digital health applications.

3. Results

3.1. The regulations and other guidance documents

The Regulation (EU) 2017/745 and Regulation (EU) 2017/746 serve as the cornerstone of the EU regulatory framework for medical devices, enhancing patient safety and device performance for the benefit of patients/users and the general public. The European Commission is still steadfastly dedicated to doing its work for the two regulations to be completely and effectively implemented. (10)

Medical Device Coordination Group (MDCG) is established under Article 103 of the Regulation (EU) 2017/745 on medical devices. One member plus one alternate (expertise in the medical devices field) and one member plus one alternate (expertise in the in vitro diagnostic medical

devices field) are appointed by each Member State for a duration of 3 years (renewable). (14, 19)

The MDCG is divided in 13 subgroups that provide advice in these fields:

- Clinical investigation and evaluation (CIE);
- Notified bodies oversight (NBO);
- In vitro diagnostic medical devices (IVD);
- Standards;
- Market Surveillance (MS);
- Post-market surveillance and vigilance (PMSV);
- Borderline and classification (B&C);
- "Annex XVI" products.
- New technologies;
- Unique device identification (UDI);
- EUDAMED;
- Nomenclature;
- International matters; (14)

They draft guidance documents related to the above-mentioned fields, and some of the related topics are included below (14).

In order that the economic operators comply with the provisions set on the Regulation (EU) 2017/745 and Regulation (EU) 2017/746, some of the guidance documents drafted by the Medical Device Coordination Group (MDCG) according to the different subjects (as divided below) include:

- On clinical investigation and evaluation, MDCG guidance documents are published related to specific questions and answers regarding the conduct of clinical investigations; on reporting (safety) in clinical investigations; documents about the application/notification regarding clinical investigations; assessment report template of clinical evaluations; summary of clinical investigation report's content and structure; template of post market surveillance clinical follow up (PMCF) plan and evaluation report; guidance on equivalence (clinical evaluation); legacy devices' sufficient clinical evidence; safety and clinical performance summary; clinical investigations' substantial modification. (13)

- On notified bodies (NBs), MDCG guidance documents are published regarding different topics, including: designation of conformity assessment bodies, re-assessment and notification; notified bodies' related requirements; guidance on certification activities for distributors, importers and notified bodies (NB); application form when applying for designation as NB under the Regulation (EU) 2017/745-MDR and Regulation (EU) 2017/746 - IVDR, submitted by a conformity assessment body; templates of preliminary assessment review (both MDR and IVDR); on significant changes and relevant surveillance related to the transitional provisions as per article 120 of the Regulation (EU) 2017/745; on hybrid audits; notes on the codes of the Regulation (EU)

2017/745 - MDR, Regulation (EU) 2017/746 - IVDR; about the information needed by those working in conformity assessment; qualification/eligibility for personnel authorization (both MDR and IVDR); on sampling of devices (technical documentation assessment); on certificates content. (13)

- On Post-Market Surveillance and Vigilance, guidance regarding the Periodic Safety Update Report (PSUR) and also about concepts and terminology on vigilance according to Regulation (EU) 2017/745. (13)

- On borderline and classification, MDCG published guidance documents are related to the medical devices classification; borderline between medicinal products and medical devices under Regulation (EU) 2017/745; procedure of Helsinki for borderline and classification under both Regulation (EU) 2017/745 and Regulation (EU) 2017/746. (13)

- On EUDAMED, guidance on legacy devices registration and registration of devices timelines in EUDAMED; rules and obligations for registration of actors other than importers, manufacturers and authorised representatives; until the full functionality of EUDAMED, guidance on standardised administrative procedures and alternative technology solutions; use of the Single Registration Number (SNR) and registration module of actors. (13)

- On European Medical Device Nomenclature (EMDN), guidance on the nomenclature of medical devices, including requirements description and general principles. (13)

- On new technologies, guidance on softwares and cybersecurity is provided by the relevant MDCG guidance documents. They include information on the conditions when a software is classified as a medical device; guidance on the clinical evaluation/performance evaluation of softwares that are medical devices; as well as classification and qualification of these softwares. (13)

- On In Vitro Diagnostic medical devices (IVD), guidance on rules of classification for in vitro diagnostic medical devices; questions and answers related to the interface between Regulation (EU) 2017/746 and Regulation (EU) 536/2014 on clinical trials for medicinal products for human use; template of the safety and performance summary; on significant changes and relevant surveillance regarding the transitional provision as per article 110 of Regulation (EU) 2017/746; clinical evidence general principles for in vitro diagnostic medical devices (IVDs); performance studies substantial modification under Regulation (EU) 2017/746 and their application/notification documents; on legacy devices requirements and devices placed on the market under Directive 98/79/EC (prior 26 May 2022); verification by notified bodies of manufactured class D in vitro diagnostic medical devices, as well as on the transitional period for the certification of these types of devices; measures that notified bodies must adhere to in light of the expert panel's consultation, as per article Article 48(6) of Regulation (EU) 2017/746. (13)

- Other MDCG guidance documents published are related to importers, distributors and authorised representatives, implant cards, custom-made and in-house devices. (13)

The list of ongoing guidance documents (in the development phase) that are in progress, is also published and updated in the European Commission's website in a constant manner, offering the general public the necessary information in this regard. (13)

According to article 8 of Regulation (EU) 2017/745, devices are presumed to be in compliance with the requirements of this Regulation covered by the relevant harmonised standards or relevant portions of these standards, references of which are published in the (OJEU) Official Journal of the European Union. Harmonised standards for medical devices in accordance with Regulation (EU) No 1025/2012, European standardising institutions CEN and CENELEC establish regulations based on standardising Requests filed by the Commission. The voluntary use of such standards confers a presumption of conformity with the regulations they seek to cover after the Commission publishes their references in the Official Journal of the European Union. (19)

The purpose of MDCG 2021-5 *Guidance on standardization for medical devices,* is to give guidance on various standards-related issues in the medical device industry in support of the requirements outlined in the relevant EU legislation. As explained in this guidance document, the adoption of standards in the medical device industry is and will always be voluntary. (19, 26)

Although these standards are voluntary, they help medical device manufacturers stay in compliance with legal obligations, but also produce quality devices. As an example, some of the ISO standards that offer instructions on certain areas related to medical devices are: ISO 14155:2020 (Clinical investigation of medical devices for human subjects - Good clinical practice); ISO 13485:2016 (Medical devices - Quality management systems - Requirements for regulatory purposes). (19, 26)

Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices have certain parts that are designed and are subject to specific national provisions in European countries (Member States). These include:

- According to article 30(2) of Regulation (EU) 2017/745 and article 27 of Regulation (EU) 2017/746, Member States may keep or enact national provisions governing the registration of companies that distribute devices (distributors) made available on their territory.
- Provisions under article 35 of Regulation (EU) 2017/745 and article 31 of Regulation (EU) 2017/746 regarding the designation, assessment and notification of conformity assessment bodies, as well as monitoring of notified bodies.
- Single-use devices may only be reprocessed and used again when authorised by national legislation and only in line with article 17 of Regulation (EU) 2017/746.

- Activities on market surveillance of medical devices and in vitro diagnostic medical devices, in accordance with article 93 of Regulation (EU) 2017/745 and article 88 of Regulation (EU) 2017/746.
- Provisions related to the fees for the activities that are set out in accordance with article 111 of Regulation (EU) 2017/745 and article 104 Regulation (EU) 2017/746.
- The Member States are also responsible for establishing the penalties that will be applied for violations of the Regulation's (EU) 2017/745 and Regulation (EU) 2017/746' provisions and for taking all necessary steps to ensure that they are carried out/implemented. These provisions are foreseen in article 106 of Regulation (EU) 2017/746 and article 113 of Regulation (EU) 2017/745. (19, 29)

The Commission will consider making appropriate adjustments if evidence suggests that the proposed regulations do not accomplish their goals or have a negative effect on public health, patient safety or innovation. In this regard, it is expected that the Commission will carry out a thorough evaluation of the Regulation (EU) 2017/745 by May 2027. (10)

3.2. Latest developments

As the medical devices field constantly evolves with new innovations and technologies, some of the latest developments and trends are changing the way diseases are detected and treated. These trends include among others artificial intelligence (AI) and virtual reality (VR) technology. A key area of the life sciences now involves the application of algorithms and machine learning in the early detection, accurate diagnosis, as well as treatment of diseases. (16)

Life science companies may continue to pave the road for access, better care, and more personalized treatment by embracing the potential of recent advancements in digital transformation. Just as AI helps personalise healthcare, it may also lead to concerns about ethics and security. Keeping patient data secure is the most important factor to take into account while collecting and sending massive volumes of data. The power of AI to support healthcare practitioners and people in making better healthcare decisions has huge value. The advantages are obvious, but the ethical ramifications can be challenging. (17)

As the market size for AI is growing, taking into account the advantages, but also the challenges regarding the ethical and security considerations, the European Commission originally suggested a legal framework for Artificial Intelligence (AI) in April 2021. Is the first time in the world that artificial intelligence will be regulated and these rules will govern how artificial intelligence in the EU is used. The aim of the EU is to regulate AI, for the better creation and application of this technology considered as ground-breaking. (15)

The goal of the Members of the European Parliament (MEPs) is to guarantee that AI systems are transparent and safe. Depending on the level of risk that the AI can produce, the rules define obligations for providers and users. The right and ability to express complaints/dissatisfaction with AI systems, as well as bans on emotion recognition and biometric surveillance are among the MEPs' demands. They also include customised rules for general-purpose AI and GPT-like foundation models. (15)

The Members of the European Parliament (MEPs) accepted the negotiation position of the European Parliament as regards the AI Act on the 14th of June 2023. By the end of the year 2023, an agreement is intended to be reached, considering the starting period of discussions with EU countries in the Council on the law's final form. (15)

3.3. Digital transformation

The digital transformation of medicine has been triggering in the last years the evidence based healthcare. While new technologies keep advancing and the medical device applications (also called digital health apps) are being ‘’built’’ very quickly, guidance documents for softwares that are classified as a medical device are developed, as mentioned above in point 3.1 of this master thesis. Going back a few years ago, reimbursing a medical app wouldn’t have been considered as a possibility and yet today is a reality. The financing and reimbursement programmes for these digital health apps that are currently in existence vary across Europe and they point out both general trends and recurring themes as well as country- or region-specific variations across Germany, Belgium, France and the Netherlands. Germany, France and Belgium were among the first countries in Europe to create a formal framework for the reimbursement of medical apps. (23)

Two countries: Germany and Belgium, are taken into consideration below while explaining their systems and legal framework in this regard. On December 19, 2019, the Digital Healthcare Act went into force, bringing for patients the so-called "app on prescription" in the healthcare system. As a result, the people who are insured by the German statutory health insurance have the right to utilise a DiGA that has been recommended/prescribed by a doctor and are reimbursed by the health insurance. DiGA; "Digitale Gesundheitsanwendungen" (in German) or digital health apps offer a variety of opportunities for the detection and treatment of diseases, as well as for promoting an active and healthy lifestyle. In order to be considered a DiGA, a medical device with the CE certification must have the following features: (22, 23, 27)

- It is a medical device of risk class I or IIa.
- The DiGA is in favor of diagnosing, monitoring, treating, or eradicating, compensating illnesses, disabilities or injuries.
- Digital technologies are the foundation of the DiGA's primary function.
- Its digital function primarily serves the medical purpose.
- The patient alone or patient and healthcare professional may utilise the DiGA. (22, 23, 27)

A DiGA must have successfully passed the BfArM evaluation in order to be listed in the DiGA directory - Directory of Reimbursable Digital Health Applications. The specifics and details of this procedure have been governed by the supplemental legislative rule issued by the Federal Ministry of Health (Bundesministerium für Gesundheit, BMG), which is the Digital Health Applications Ordinance. (22, 23, 27)

The assessment process: The BfArM must evaluate the DiGA within a maximum of three months after the entire application has been filed. The focus of this evaluation is on the

manufacturer's evidence of the product's attributes, including data protection, interoperability, and user friendliness, as well as the manufacturer's own documentation of the DiGA's beneficial effects on healthcare. These are the ways in which the usage of the DiGA improves a patient's state of health or his or her capacity to treat their disease. (22, 23, 27)

The submission regarding the fast-track DiGA procedure is done through the electronic portal link: BfArM application portal. The electronic portal's purpose is to assist in managing BfArM applications and notifications and to give the greatest assistance possible when submitting them. In Germany, as part of the healthcare system, the government already pays for 31 medical applications. (22, 23, 27)

A legal framework has been in place in Belgium since January 2021 for the reimbursement of medical applications. The "mHealthBelgium validation pyramid" is a project of the publicprivate platform mHealthBelgium, which seeks to assist both healthcare professionals and patients through the proliferation of apps and to make it apparent to businesses what requirements medical applications must achieve in order to be sold in Belgium. Practically speaking, it is a graphic representation of the three layers of particular criteria set out by the Belgian government as the "validation" process. The criteria are developed in consultation with three national authorities:

- The Federal Agency for Medicine and Health goods (FAMHP), which is level M1 of the validation pyramid's competent authority and is in charge of evaluating the efficacy, quality, and safety of medicines and other products, such as medical devices;

- The eHealth Platform, which is the federal institution in charge of creating the infrastructure for digital health for ensuring that devices are securely linked and exchanging information in the healthcare industry (level M2 of the pyramid of validation);

- The National Institute for Health and Disability Insurance (NIHDI) is the competent authority in charge of the payment of healthcare supplies and services (pyramid level M3). (22, 27)

Fig. 2 below shows the 3 levels of the mHealth validation pyramid in Belgium

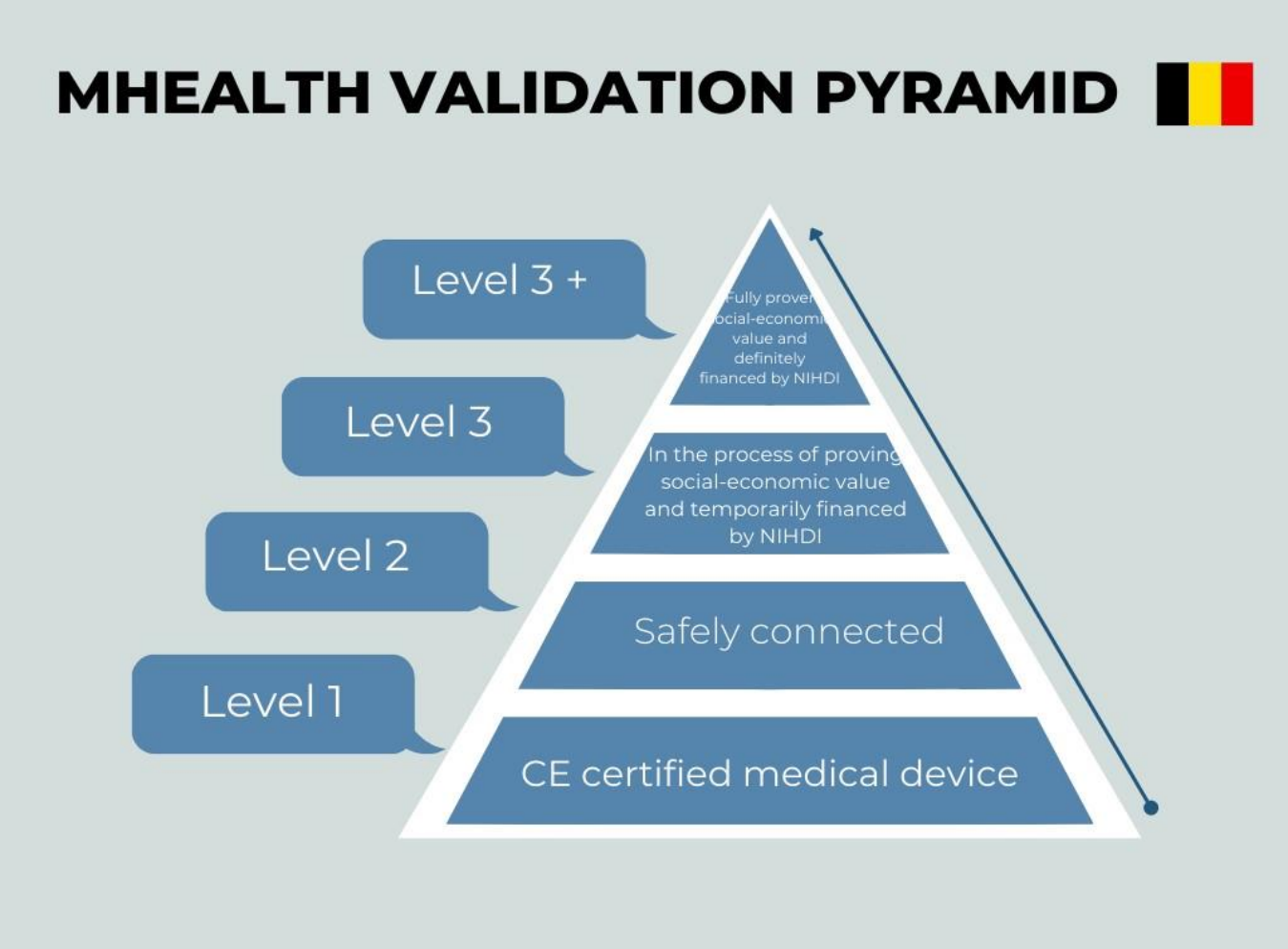

Fig.2. The mHealth pyramid in Belgium. (Source: Belgian platform for medical mobile applications: mHealthBELGIUM. *Pyramid chart made with Canvas*) (27)

During their recovery, individuals who have a knee or hip prosthesis are supported by the application MoveUP. MoveUP is the first app in level M3 mHealth validation pyramid in Belgium. Other applications for level M3 financing are also planned. Since then, the government has given two of them favorable reviews: one for cancer and one for sleep therapy. It is essential that an app can be seen in the context of a larger care process at all times. The government is anticipated to reconsider numerous health care procedures in the next months in order to formally recognise the usage of medical apps and other types of digital health technology. (27)

The initiatives of these countries aim to support patients in preventative care, treatment, and recovery by assisting them in improving their lifestyles, treating their medical problems. They are already highly well-liked among patients and people in Europe. In an effort to standardise such funding, numerous European nations and regions have launched special funding programmes for health applications in recent years. (23)

4. Discussion

The European Union constantly implements initiatives that foster research and innovation in different areas, including the sector of medical devices. To guarantee patient safety, as well as greater protection of the public health, the Regulation (EU) 2017/745 and the Regulation (EU) 2017/746 built a more robust and modernised EU legislative framework, while fostering the sector's modernization and strengthening the EU's position as a worldwide leader in the industry. (11, 28)

The implementation of the new provisions has made significant progress, although the transition has taken longer than expected. The EU's healthcare systems can have the risk of having a shortage of patients' access to life-saving medical devices. Among these needs and challenges currently faced in the medical devices sector regarding orphan and paediatric medical devices are the ones related to the risk of exit from the market of these devices in the EU. Concerns regarding the return of investment for manufacturers (especially small and medium enterprises) impact the availability of medical devices, as they target a small group of patients and as a consequence, also the research and development of these devices will also be reduced, depriving the patients from innovative medical devices. As a consequence, the paediatric and rare diseases community in the EU faces challenges related to the lack of continuous availability of essential medical devices that are sometimes indispensable for them. (11, 28, 37)

Notified Bodies' limited capacities and the lack of readiness on the part of market operators are some of the challenges that need to be addressed related to the shortages of medical devices. Enhanced coordination among notified bodies and competent authorities as well as procedure effectiveness and administrative burden reduction are among the fields that the European Commission has been supporting the transition in this regard. Specifically, in order to mitigate the risks related to the risk of exit of orphan devices and paediatric devices and ensure that the patients can have access to these safe medical devices, relevant incentives (similar to orphan medicinal products) to stimulate the research and development of these devices and a regulatory approach/framework that can support the development and certification of orphan medical devices may be necessary. (11, 28, 37)

On the other hand, among the long-term strategies for a successful transition that are taken into consideration by the EU institutions are:

- solutions that are specific to orphan devices
- the Enterprise Europe Network's targeted assistance for small and medium enterprises (SMEs)
- pilot project on clinical development strategies for high-risk devices using scientific advice (11, 28)

Among EU funding programmes that play a crucial role in this regard is the EU4Health programme. Examples of the financial support through this programme include:

- Survey on the status/progress of implementation
- Programme to assist/support orphan devices, with a focus on paediatrics

- Joint market surveillance action
- Support for stronger Notified Bodies Coordination Group (NBCG) coordination
- Grant for notified bodies to expand their capacities, facilitated access of SMEs to notified bodies and increased preparedness of manufacturers
- Study on innovation and governance (11, 28)

As a result, the framework of EU4Health programme aims to support a number of initiatives, including those that seek to promote the development of new and current notified bodies' capacities, to make it easier for small and medium-sized businesses (SMEs) and to improve manufacturers' readiness on this regard. (10)

Horizon Europe is another program, a research one that addresses among others topics such as lifelong health, technologies and digital solutions for health and care with the overall aim of promoting health-related research. CORE-MD is one of the European Union Horizon 2020 projects that will last from April 2021 until March 2024. In order to advise EU authorities and advocate an optimal balance between safety, innovation, and clinical efficacy, it will examine methods for evaluating high-risk medical devices. (12)

The revision of the guidance on relevant surveillance and significant changes under Regulation (EU) 2017/745; on device sampling; the potential for notified bodies to issue certificates that may be subject to conditions; clarification on the type of dialogue that should take place between manufacturers and notified bodies before and during the certification process (without being considered as a consultancy), as well as the provision of additional guidance regarding the practical application for aspects and requirements related to clinical evidence of legacy devices, are all other actions that are still being worked on. (10)

As mentioned above, a lot of initiatives in this regard are being undertaken at EU level, to mitigate this risk, that all the patients, especially paediatric ones, as well as the ones that suffer from rare diseases will be able to benefit from the availability of medical devices in Europe. (30) These initiatives have specific goals that can promote and facilitate medical device innovation as well as increase cooperation between regulators and innovators. (31, 32, 33)

Concluding, we are all aware of the benefits of the medical devices (MDs) and in vitro diagnostic medical devices (IVDs) in the lives of the patients and their users, by offering solutions for the prevention, diagnosis, treatment, monitoring, prognosis, or amelioration of diseases and playing in this way a crucial role in saving lives. Key aspects are the safety and performance of these devices, but also the possibility that the patients can have access to innovative devices.

The competitive and creative aspects that characterise the medical device industry in Europe are also due to the active participation of small and medium-sized enterprises (SMEs) in the sector. All the actors and stakeholders involved at all levels play an essential role by ensuring the proper functioning of the system. (30)

In particular, the efforts to increase alignment and innovation are implemented with significant help from regulatory authorities. The comprehension of the current regulatory requirements,

the identification of potential gaps and the evaluation of new developments in the field of innovation and technology is constantly integrated into the regulatory landscape. (36)

The evaluation of the best available evidence and the selection of policy alternatives that address these difficulties have proven to be helpful in ensuring that regulatory systems keep up with advances in the technology and science that they control. (35) The involvement of stakeholders, and their ongoing cooperation with regulatory authorities during these years has also had results on:

- Improvement of the ability to foresee the challenges posed by new emerging technologies or innovations that could speed up patient/user access
- Considering the complexity of the interactions between legislation and innovation
- Evaluating potential impact on patient/user care
- Identifying various policy solutions that may be used to solve several challenges
- Constantly updating medical device legislation to reflect advances in technology.

(34)

The legal framework for medical devices in the EU ensures the operation of the industry, with strong patient health protection as the cornerstone. Present and future developments in the field are expected to transform the industry and the system in the upcoming years and we are eager to witness the revolutionization. (30)

5. Acknowledgments

The EMOTION master has been for me one of the most challenging and yet greatest experiences so far. During this journey, I have had the possibility to acquire knowledge and gain experience also in areas that I haven't explored before, as well as meet people that I can consider as my best friends. I would definitely consider it as a once in a lifetime experience.

I would like to thank the coordinator of the programme Prof. Genazzani for giving me the opportunity to be part of the EMOTION master and for its support during the programme and our stay in Italy. A special thanks goes also to Prof. Jean-Pierre, the supervisor of the master thesis for its guidance and coordination during the semester spent in Namur, Belgium. I would also like to thank my mentor of the traineeship performed at the European Commission, Mr. Paul Piscoi for its support while I was engaged in the work of the Unit responsible for medical devices.

A big appreciation goes to all the professors of Università degli studi del Piemonte Orientale and Université de Namur for their professionalism and patience towards us and of course to the colleagues part of this master and all the friends that I have had the opportunity to make during the duration of the program, as an important part of this adventure that we have enjoyed and shared together.

Of course, all of this would have not been possible without the encouragement, constant presence and support of my family during this academic journey. In particular, I dedicate this achievement to my mom, the strongest, yet kindest person; role model and true inspiration for pushing me to never give up on my dreams.

P.S: Be the hero of your own story.

6. References:

1. Annual value of the medical devices market in Europe from 2021 to 2027, Statista website, Accessed 2 August 2023. URL: https://www.statista.com/statistics/1350975/european-medical-devices-market/
2. Greg Roughan, The Medical Device Industry in 2020-2023: Key Trends & Outlook, 17 December 2020. Unleashed software website. Accessed 5 August 2023. URL: https://www.unleashedsoftware.com/blog/the-medical-device-industry-in-2020-2021-key-trends-outlook
3. Medical device outlook for 2023 and beyond, Wolters Kluwer website, 11 December 2019, Accessed 9 August 2023. URL: https://www.wolterskluwer.com/en/expert-insights/medical-device-outlook
4. Nicole Scholz - EPRS | European Parliamentary Research Service, Medical devices and in vitro diagnostic medical devices, January 2017. Accessed 11 August 2023. URL: https://www.europarl.europa.eu/RegData/etudes/BRIE/2017/595881/EPRS_BRI(2017)595881_EN.pdf
5. Poly Implant Prothèse, Wikipedia website, Accessed 11 July 2023, URL: https://en.wikipedia.org/wiki/Poly_Implant_Proth%C3%A8se
6. PIP Action, The PIP action website, Accessed 12 July 2023, URL: https://pipaction.net/the-pip-scandal/
7. PIP action plan, The European Commission website, Accessed 11 July 2023, URL: https://health.ec.europa.eu/medical-devices-sector/directives/pip-action-plan_en
8. Medical devices, new regulations, overview, European Commission website, Accessed 5 August 2023. URL: https://health.ec.europa.eu/medical-devices-new-regulations/overview_en
9. Regulation (EU) 2023/607 amending Regulations (EU) 2017/745 and (EU) 2017/746, EurLex website, Accessed 7 August 2023. URL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0607
10. Note from the General Secretariat of the Council to the Council of the European Union, Subject: Implementation of the Medical Device Regulation - Information from the Commission, 6 December 2022. Council of the European Union website. Accessed 9 August 2023. URL: https://data.consilium.europa.eu/doc/document/ST-15520-2022-INIT/en/pdf
11. Christian Kurrer / Nicoleta Lipcaneanu: Medicines and medical devices – Fact sheets on the European Parliament, European Parliament website, April 2023, Accessed 8 August 2023, URL: https://www.europarl.europa.eu/factsheets/en/sheet/50/medicines-and-medical-devices
12. About the initiative, CORE-MD website, Accessed 12 August 2023, URL: https://www.core-md.eu/ , Horizon Europe, about the programme, European Commission website, Accessed 12 August 2023, URL: https://commission.europa.eu/funding-tenders/find-funding/eu-funding-programmes/horizon-europe_en
13. Guidance - MDCG endorsed documents and other guidance, European Commission website, Accessed 11 August 2023, URL: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

14. Medical Device Coordination Working Groups, European Commission website, Accessed 18 August 2023, URL: https://health.ec.europa.eu/medical-devices-dialogue-between-interested-parties/medical-device-coordination-group-working-groups_en
15. EU AI Act: first regulation on Artificial Intelligence, European Parliament website, Created 8 June 2023 (Updated 14 June 2023), Accessed 20 August 2023, URL: https://www.europarl.europa.eu/news/en/headlines/society/20230601STO93804/eu-ai-act-first-regulation-on-artificial-intelligence
16. 5 innovations that are revolutionizing global healthcare, World Economic Forum website, 22 February 2023, Accessed 24 August 2023, URL: https://www.weforum.org/agenda/2023/02/health-future-innovation-technology/
17. Mike Tendick, Jenna Joestgen, Megan Schleicher, Medical Device Industry Trends: 2023 and Beyond, Plexus website, Accessed 7 August 2023, URL: https://www.plexus.com/en-us/current/articles/medical-device-industry-trends
18. Importance of medical devices in healthcare: Their Uses & Key Emerging Technologies, Feb 15, 2023, RegDesk, Inc website, Accessed 15 August 2023. URL: https://www.regdesk.co/importance-of-medical-devices-in-healthcare-their-uses-key-emerging-technologies/
19. Regulation (EU) 2017/745 on medical devices. EurLex website, Accessed 12 August 2023. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
20. Medical Device Directive 93/42/EWG (MDD), Johner institute website, Accessed 27 August 2023, URL: https://www.regdesk.co/importance-of-medical-devices-in-healthcare-their-uses-key-emerging-technologies/
21. History of medical devices, Eupati Website, Accessed 15 August 2023. URL: https://learning.eupati.eu/mod/page/view.php?id=927&forceview=1 ; Manufacturers of devices without an intended medical purpose, European Commission website, Accessed 5 August 2023. URL: https://health.ec.europa.eu/medical-devices-topics-interest/reprocessing-medical-devices/manufacturers-devices-without-intended-medical-purpose_en
22. Digital Health Applications, BfArM website, Accessed 20 August 2023, URL: https://www.bfarm.de/EN/Medical-devices/Tasks/DiGA-and-DiPA/Digital-Health-Applications/_node.html , DiGA_Guide (1).pdf
23. Position paper: Recognising the value of digital health apps: An assessment of five European healthcare systems, 19 November 2021, MedTech Europe website, Accessed 15 August 2023, URL: https://www.medtecheurope.org/wp-content/uploads/2021/11/2111_v4.8_mte_dht_reimbursement16.11.2021-2.pdf
24. EUDAMED overview, European Commission website, Accessed 27 August 2023, URL: https://health.ec.europa.eu/medical-devices-eudamed/overview_en
25. MDCG 2020-16 rev.2: Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746, February 2023, Published on the European Commission website, Accessed 15 August 2023, URL: https://health.ec.europa.eu/system/files/2023-02/md_mdcg_2020_guidance_classification_ivd-md_en.pdf
26. Tom Rish, Ultimate List of ISO Standards for Medical Devices, 14 July 2023, Accessed 6 August 2023, Greenlight website, URL: https://www.greenlight.guru/blog/iso-standards
27. European mHealth Hub, Assessment Frameworks, mHealth Hub website and mhealth Belgium website, Accessed 14 August 2023, URL: https://mhealth-hub.org/assessment-frameworks , https://mhealthbelgium.be/ , https://mhealthbelgium.be/news/persbericht-duidelijk-financieringskader-nodig-voor-doorbraak-medische-apps-in-belgie-4

28. European Health Union: Supporting the transition to the new medical device framework (factsheet), European Commission website, Accessed 9 August 2023, URL: https://health.ec.europa.eu/system/files/2023-01/mdr_proposal_factsheet_0.pdf
29. Regulation (EU) 2017/745 of the European Parliament and the Council on in vitro diagnostic medical devices, EurLex website, Accessed 2 August 2023, URL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746
30. Medical devices sector overview, European Commission website, Accessed 3 August 2023, URL: https://health.ec.europa.eu/medical-devices-sector/overview_en
31. Innovation in medicines | European Medicines Agency (EMA) website, Accessed 21 August 2023, URL: https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines
32. Food and Drug Administration Safety and Innovation Act (FDASIA) | FDA
33. Revision of the Cosmetic Products Regulation (EC No 1223/2009) following the EU Chemicals Strategy for sustainability, Publications Office of the European Union website, Accessed 29 August 2023, URL: https://op.europa.eu/en/publication-detail/-/publication/3b63422e-2c4c-11ec-bd8e-01aa75ed71a1/language-en
34. OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris.
35. The Future of Pharmaceutical Innovation: New Challenges and Opportunities - By James Mittra, Joyce Tait and David Wield at the Economic and Social Research Council (ESRC) Innogen Centre
36. Annual Report 54th analysis of the cosmetics industry and consumption in Italy in 2021 - Cosmetica Italia
37. Open letter to Commissioner (27/6/2023): U*rgent action needed to secure continued access to essential medical devices for children and for patients with orphan diseases.* Accessed 9 August 2023 URL:https://www.espr.eu/_download/Letter_Kyriakides_Med_Devices_signed_270623.pdf?m=1688374800&