Bachelor's thesis

Business Administration

2019

Thaís Mikkola

GUIDELINE FOR FOLLOWING THE LATEST MEDICAL DEVICE REGULATION

- Case: Wellbeing Analytics company

TURKU AMK
TURKU UNIVERSITY OF APPLIED SCIENCES

BACHELOR'S THESIS| ABSTRACT

TURKU UNIVERSITY OF APPLIED SCIENCES

Business Administration

2019 | 50 pages and appendices

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GUIDELINE FOR FOLLOWING THE LATEST MEDICAL DEVICE REGULATION:

Case: Wellbeing Analytics Company

Over the past years, there have been raising expectations concerning quality, security, and effectiveness of the Medical Device Regulation. With new technology emerging - and after - scandals threatening the health of thousands of patients, the authorities recognized the need to take more stringent measures for the safety of patients and users of medical devices. The new Medical Device Regulation (EU) 2017/745 aims to set even higher standards of quality and safety compared to the currently used Directives.

When the new Regulation came valid on May -2017, many products - regulated before under the Medicine Legislation began to be regulated under the MDR, forcing manufacturers to perform an audit and review each of their devices and all the processes involved in the device's life cycle to achieve compliance with the new Regulation. (MHRA, 2017) For new enterprises, with limited resources, the route of conformity can be a significant challenge. This thesis acts as a guideline for manufacturers who aim to register their product as a medical device. Based entirely on the new Medical Device Regulation (MDR), this study intends to facilitate the reading of the Regulation, explaining the key points to consider before, during and after placing the medical device on the market or putting into service.

The thesis followed a qualitative research approach with methods such as document analysis and company analysis. The European Medical Device Regulation was analyzed in the context of a wellbeing analytics company. Finally, practical conclusions are presented to help the company complying with the Regulation. The purchase of a Quality Management System Standard was one of the suggestions given as a strategy to facilitate the development of a new product to comply with the regulations.

KEYWORDS:

Medical Device Regulation, Medical Device, software as a medical device, Quality Management System, SaMD, MDR, QMS.

OPINNÄYTETYÖ AMK | TIIVISTELMÄ

TURUN AMMATTIKORKEAKOULU

Liiketalous

2019 | 50 sivua, liitesivu

Thaís Mikkola

OHJEET UUSIMMAN LÄÄKINNÄLLISTEN LAITTEIDEN SÄÄNTELYN NOUDATTAMISEKSI

Case: Hyvinvointianalytiikkayritys

Viime vuosien aikana sääntelyviranomaiset ympäri maailmaa ovat nostaneet laatua ja vaatimustenmukaisuutta koskevia odotuksia. Uusista lääkinnällisistä laitteista annettu asetus (EU) 2017/745 tuli voimaan toukokuussa 2017 ja sen tavoitteena oli asettaa entistä korkeammat laatu- ja turvallisuusvaatimukset verrattuna nykyisiin direktiiveihin.

Kun lääkinnällisten laitteiden asetus tuli voimaan, monia tuotteita, joita aiemmin säänneltiin lääkkeitä koskevassa lainsäädännössä, alettiin säännellä lääkinnällisten laitteiden asetuksen alla. Tämä pakotti valmistajat itseauditointiin- ja tarkastelemaan prosesseja uuden asetuksen noudattamiseksi.

Uusille yrityksille, joilla on rajalliset resurssit, reitti vaatimustenmukaisuuteen voi olla suuri haaste. Tämä opinnäytetyö toimii ohjeena valmistajille, jotka haluavat rekisteröidä tuotteensa lääkinnällisenä laitteena. Perustuen täysin uuteen lääkinnällisiin laitteisiin sovellettavaan asetukseen (MDR), tämän työn tarkoituksena on helpottaa asetuksen lukemista selittämällä keskeisiä seikkoja, jotka on otettava huomioon ennen lääkinnällisen laitteen markkinoille saattamista, sen aikana ja sen jälkeen.

Opinnäytetyössä noudatettiin laadullista tutkimusmenetelmää, jossa on käytetty menetelmiä, kuten asiakirjojen analysointi ja yritysanalyysi. Eurooppalainen lääkinnällisten laitteiden asetus analysoitiin hyvinvointi analytiikka yrityksen näkökulmasta. Lopuksi esiteltiin käytännön johtopäätöksiä auttamaan yritystä vastaamaan asetuksia.

Laadunhallintastandardin ostaminen oli yksi ehdotuksista, jotka annettiin strategiana helpottamaan uuden tuotteen kehitystä vastamaan asetuksia.

ASIASANAT:

Lääketieteellisten laitteiden sääntely, lääketieteellinen laite, ohjelmisto lääketieteellisenä laitteena, laadunhallintajärjestelmä, SaMD, MDR, QMS.

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LIST OF ABBREVIATIONS

CE	Conformité Européenne
EU	European Union
Eudamed	European database on medical devices
MD	Medical device
MDD	Medical Device Directive
MDR	Medical Device Regulation
MEDDEV	European guidance by European Commission
MHRA	Medicines and Healthcare products Regulatory Agency
NB	Notified Body
QMS	Quality Management System
SaMD	Software as a medical device
SME	Small and Medium-sized Enterprise
UDI	Unique Device Identification
ISO 13485:2016	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO 14971:2012	Application of risk management to medical devices
ISO 14155:2011	Clinical investigation of medical devices for human subjects - Good clinical practice
IEC 62304:2006	Medical Device Software - Software life cycle processes

1 INTRODUCTION OF THE TOPIC AND RESEARCH PROBLEM

Creating and developing a new medical device, in Europe, requires more than just a good idea and excellent engineering. Before launching a new medical device in Europe, companies are required to provide technical documentation giving evidence that they follow the “regulatory framework, which ensures a high level of safety and health while supporting innovation” (Regulation (EU) 2017/745).

Regulations are a set of documents designed to ensure that medical device companies and all parties involved such as manufacturers, conformity assessment bodies, authorities, and professional users meet performance and safety requirements to protect patients and third parties from hazards and frauds.

To meet the requirements companies, need to understand their device and revise the specifications required by the authorities to determine which laws best apply to the case.

On the 25th of May 2017, two new regulations on medical devices were adopted. Medical Devices Regulation (EU) 2017/745 and the *in vitro* Diagnostic Medical Devices Regulation (EU) 2017/746 are replacing the existing Medical Device Directives (Directive 93/42/EEC; Directive 90/385/EEC; Directive 98/79/EC) and are setting even higher standards for quality and safety. (European Commission 2016)

Benete, the case company, has been developing an upgradeable platform compatible with any device capable of transmitting valuable information about the physical and mental well-being of the elderly. The “Life Analytics Platform,” is the software itself and operates generating data by a variety of technology ambient sensors to create patterns of an individual’s daily activities and routines.

Life Analytics captures all the data to generate a complete view of the senior's life condition. The software collects, processes, stores the data and sends it for analysis enabling healthcare professionals, and relatives follow the Senior’s action. The data acquired can be used to promote personalized care.

In the present circumstance, the company’s software is not a medical device. However, being able to monitor and provide information that can be used to make decisions about

the elderly are some of Benete's long-term goals, and this classifies it as a medical device under the Regulation. Therefore, the company must comply with the MDR.

The goals are to define which route the case company needs to follow once the software crosses the borderline and becomes a medical device. Moreover, provide more knowledge about the new Medical Device Regulation by describing key concepts presents before, during and after placing a medical device on the market or putting into service, helping the company comply with the requirements established by the regulation.

This thesis addresses a common problem faced by healthcare software companies: "How to create a compliance trail that supports the safety and quality requirements proposed in the Medical Devices Regulation when the software is not yet considered a medical device." The result of this thesis is to explain important aspects of the new Medical Devices Regulation and to create a compliance route that considers the company' situation.

The theoretical base continually refers to the new Medical Device Regulation, citing the annexes and recitals present on it. The thesis describes essential requirements to obtain compliance with the Medical Device Regulation, considering the case company. The terms "new regulation," "MDR," "Regulation" is used as an alternative to address the Medical Devices Regulation (EU) 2017/745.

Through this thesis and background work, Benete will understand what is required by the regulations and what kind of steps the company should follow to obtain compliance.

2 MEDICAL DEVICE REGULATION

In the business world, it is common for some enterprises to rush up to launch a new product on the market without making lengthy preliminaries. This race should not occur in the health sector for safety reasons.

The critical factor in producing a new medical device is to ensure that the product outweighs the risks created by exposing the device to the patient. (Ramakrishna, Tian et al., 2015 p.11) This precaution is to improve the quality, security, and reliability of the medical device and, increase the transparency of information for consumers as explained in the Regulation.

The book: "Medical Devices: Regulations, Standards, and Practices" cites the different regulatory authorities in each country. The figure below is an image adapted from table 1.5 and figure 1.9 presented in the book (Ramakrishna, Tian, et al., 2015 p.14,15). The figure helps to illustrate the regulatory authorities around the world.

Figure 1 The biggest Regulatory authorities around the world.

Each of these authorities recognizes the devices based on the complexity of the device, the intended purpose of use and the level of risk ranging from low to high risk. High-risk

devices require tighter control measures to ensure proper and safe use. (Ramakrishna, Tian, et al., 2015).

In Europe, the CE mark is required to allow the free movement of products on the European market. For companies to obtain the CE mark, they need to ensure that their products comply with health, safety, and environmental protection standards. (Ramakrishna, Tian, et al., 2015).

However, before looking further into the regulations matters, the manufacturers must understand the definition of medical device, the changes made in the new regulation and be aware of the transition time.

2.1 Medical Device definition

The medical device (MD) is a healthcare product that plays an increasing role in patient care. The term “medical device" is quite comprehensive and covers a vast range of apparatus from something simple as bandages and thermometers to advanced devices such as computers software, and implants. Such products are used to diagnose, monitor, prevent and assist people with disabilities or treat diseases, whether acute or chronic. Without medical devices, any surgical intervention would not be possible. (Regulation (EU) 2017/745)

2.2 In Europe, the MDR (EU) 2017/745 defines a medical device as:

> *“An instrument, apparatus, appliance, software, implant, reagent, apparatus, 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 a physiological or pathological process or state; Providing information using in vitro examination of specimens derived from the human body, including organ, blood and tissue donations.This definition includes devices that do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means -- but which may be assisted in its function by such means.”* (Regulation (EU) 2017/745)

2.3 Software as a medical device (SaMD)

The Medical Device Guidance document (MEDDEV 2.1/6, 2016) describes "Software" as a collection of instructions that processes input data and generates output data. The

document also specifies "Standalone software" as a software which is not combined in a medical device, and the term "Software as a Medical Device" (SaMD) is explained as software which has one or more medical purposes without being integrated into another medical device. (MEDDEV 2.1/6, 2016)

The decision diagram (Figure 2) provides direction whether the device should be considered medical device software or not. It is an adaptation of the diagram presented in the Medical Device Document mentioned above (MEDDEV 2.1 / 6, 2016).

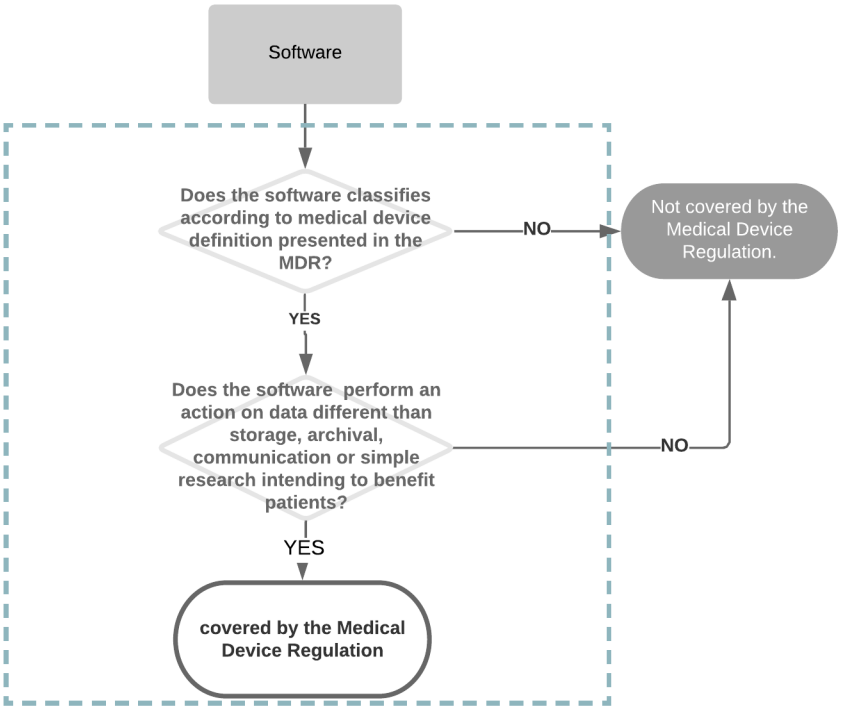

Figure 2 Decision diagram to Classify software as a medical device.
Edited (MEDDEV 2.1 / 6, 2016)

2.4 Medical Device Classification

As shown in figure 1, medical device regulations differ worldwide. In Europe, the classification of the medical device is outlined in Annex VIII of the Medical Device Regulation. Moreover, there are four safety classes:

- **Class I -** low risk

- **Class IIa -** medium risk
- **Class IIb -** medium risk - high
- **Class III** - high risk

For learning purposes, there are at least twenty-two classification rules divided among invasive devices, active devices, non-invasive devices, and special cases. Software, as outlined in Annex VIII, is an "Active Device" independent of its participation, alone as Stand-alone software (SaMD) or in combination with other medical devices. (Regulation (EU) 2017/745)

According to the regulation, the rule that applies to software is Rule 11. This rule is intended for software that can provide information that enables the detection, diagnosis, monitoring, and treatment of adverse physiological and health conditions such as diseases or congenital deformities. (Annex VIII, Regulation (EU) 2017/745)

The software class differs from the level of risk. The software is classified as Class IIa - when it provides information that is used to make decisions concerning diagnostic or therapeutic purposes. But, it will be classified as class IIb if such decisions could lead to aggravate the state of health of a person or cause some surgical intervention. However, if the impact of software use can lead to the death or irreversible deterioration of a person's health status, then the software is considered class III. (Annex VIII, Regulation (EU) 2017/745)

Also, a device which is designed to monitor physiological processes is listed as class IIa, unless the software is intended to monitor vital physiological parameters, and the variations of these parameters may cause an immediate hazard to the patient, so the software is classified as class IIb. The other software is classified as class I. (Annex VIII, Regulation (EU) 2017/745)

As can be noted, the classification rules of the Regulation analyze the intended purpose of the medical device and the level of risk it may present to the patient or the person handling it. The intention to determine the classification is to ensure an adequate level of supervision and validation. Besides, it is analyzing the duration of the medical device in the body and their invasive character. (Roldán and Manuel 2016);(Regulation (EU) 2017/745)

The MD classification will determine the appropriate conformity assessment route that manufacturers must follow to demonstrate compliance with the new MDR. The

interference and level of control that the external parties will have on the device is associated with the risk level associated with the device. (Emergo, 2018)

The Declaration of Conformity (DC) is one of the last steps to ensure that medical devices can be placed on the market. The Declaration can be issued by the Notified Body (NB), which may be a public or private organization, created by the national Competent Authority, designed to perform as third-party conformity, providing assessment activities, including calibration, testing, certification, and inspection. Although some Class I devices do not need an NB to issue the Declaration of Conformity, which means that the manufacturer can self-declare. (Regulation (EU) 2017/745)

2.5 Changes in the new medical device regulation

Over the last years, there have been raising expectations concerning quality, security, and effectiveness of regulation. With new technology emerging early and after witnessing some scandals that threaten the health of thousands of patients, the authorities recognized the need to take more stringent measures for the safety of patients and users of medical devices. The medical device manufacturers themselves appeared to recognize the relevance of creating an excellent reputation for ethical behavior, compliance, quality, and value. (Manz, 2018)

In the United States, the FDA (Food and Drug Administration) oversees all regulations of medical devices. In Europe, the regulatory bodies for medical devices are European Commission (EC), governmental Competent Authority (CA), Notified Bodies (NBs), responsible for overseeing device evaluation, market approval, and post-market surveillance. (Ramakrishna et al. 2015)

Since the 1990s until 2008, few changes were made concerning the laws for medical devices. When new technologies emerged, few scandals appeared and forced the regulators to trigger a complete update of the laws. The changes considered: the pre-market review, monitoring, post-market monitoring and surveillance, and some information provision on devices and regulatory process. (Ramakrishna et al. 2015)

The most famous scandal was about breast implants from the French company PIP (Poly Implant Protheses), in 2011, and had far reached effects. The manufacturer intentionally used industrial-grade silicone in the implants instead of medical grade silicone. Authorities in France advised over 30,000 women to remove breast implants. More than

400,000 women around the world believed to have received industrial silicone. In the end, over 125,000 women made the delicate decision to have the implants removed. Since then, The European Commission and member states created an action plan focused on making readjustments of the old Directives. (Manz, 2018)

Currently, the medical industry is in the transition stage, moving from 3 Directives to 2 new Regulations. For companies that want to regulate their devices according to the new regulation, will notice that the present regulation has become more demanding than the previous version, but despite the reform made, to strengthen the security and transparency of the products distributed in the EU market, the product classification remains similar as described in the old Directives. The significant changes are seen in the IVDR regulation. (Manz, 2018)

2.6 Transition time for Medical Device Regulation

Both regulatory frameworks, the (EU) 2017/745, Medical Device Regulation (MDR) and (EU) 2017/746, In-Vitro Diagnostic Regulation (IVDR), was finally revised, in the second quarter of 2017. The MDR becomes active by May 2020, while IVDR as a longer transition duration, by the end of May 2024 (European Commission, 2016). Manufacturers will have a transition period to adjust to the regulation, which grants companies the time required to perform an audit and review each of their devices to reach conformity. Note that consultants and Notified Bodies will get busier as the deadline draws closer. So, to avoid market disruption, it is recommended to start the transition as soon as possible. (MHRA, 2017)

The image below shows the transition time for the Medical Device Regulation. The figure is an adaptation of the image present on the “Medicines and Healthcare products Regulatory Agency: Medical devices: EU regulations for MDR and IVDR.” (MHRA, 2017)

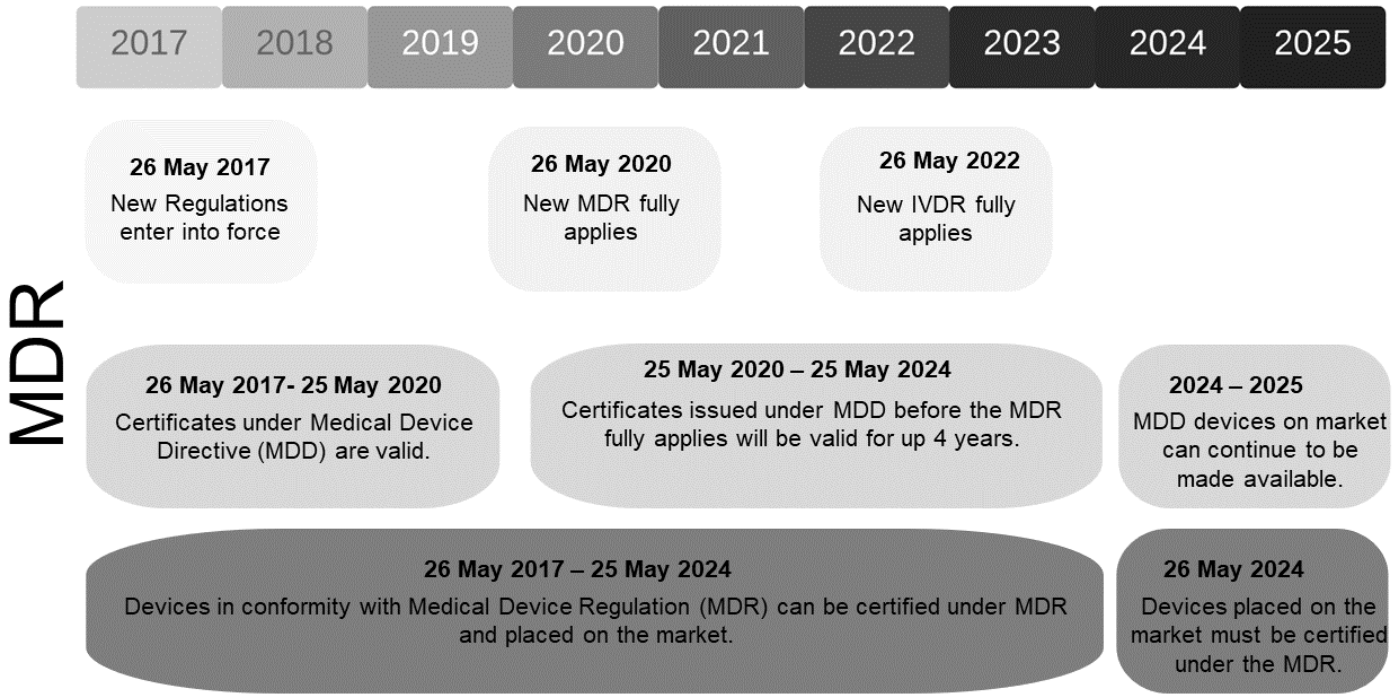

Figure 3 Transition time for medical device regulation. Edited (MHRA, 2017)

The illustration shows the deadline of each critical aspect of the new regulation allowing the companies to plan ahead when they renew the technical documentation and processes to meet the new requirements.

Through the transition period, according to MHRA (2017) devices can be placed on the European market following the current EU Directives. However, from May of 2020, new devices intended to be marketed in Europe shall comply with the new Medical Device Regulation (EU 2017/745). To be noted that medical devices with a valid CE marking may continue to be used until its expiry, even if they comply with the old 93/42 / EEC Directives. (MHRA, 2017)

3 REQUIREMENTS FOR THE MEDICAL DEVICE REGULATION: ROUTE OF CONFORMITY

The following section helps manufacturers to understand conformity assessment routes. Each stage involves several items which need to be considered before progress can be made with the device. In fact, even after achieving market approval, it is necessary to continually review and test the device to maintain safety and effectiveness.

The compliance route is influenced by the device class and by the type of 'economic operator' and its responsibilities. An economic operator, according to the Regulation (Article 2.35), can be any person who presents itself as a manufacturer, an authorized representative, an importer or a distributor, for example (Regulation (EU) 2017/745).

The manufacturer, on the other hand, is a person or a group of individuals who manufactures, repairs or fully refurbishes - creating a new device from used one - and who is responsible for put the device on the market under its name or trademark (Regulation (EU) 2017/745). For this thesis, it will be considered the manufacturer's responsibilities.

The regulatory restrictions are made to ensure the health and safety of the patients and the users, avoiding disasters such as mentioned in section 2.4 of this thesis. The limitations also serve to ensure that medical device manufacturers follow the specified procedures during the planning, production, and marketing of the device (Ramakrishna et al., 2015). The general requirements applicable to the medical device can be found at Annex I of the new Regulation.

Petri Pommelin (2018), author of "The survival guide to Eu Medical Device Regulation" strongly recommends studying the definition of the key concepts before beginning read the regulations. And it is wise advice. The description of the critical elements is placed in Article 2 of the Regulation.

For practical purposes, the most significant step to comply with the Medical Devices Regulation is to understand the device itself. Many manufacturers have difficulty with interpreting whether the device should be considered a medical device or not(MHRA, 2015).

When the MDR came into force, many products that before were regulated under the Medicines Legislation began to be regulated under the MDR to accommodate the Medical device market better. The Medicines & Healthcare products Regulatory Agency (MHRA) had created a document, available online, that set up the borderlines between medical devices and medical products (MHRA, 2015).

Another common mistake made by manufacturers is to assume that the legislation issued in their country will also be applied globally. Despite efforts to achieve global harmonization of regulatory practices for medical devices, there are still national health policies, laws and regulations established to regulate medical devices in each country (Ramakrishna et al., 2015).

The image of the world map (figure 1) shown at the beginning of this thesis displays the different regulatory authorities at the global level. This implies that if the manufacturers aspire to market their device in another country, it is necessary to verify which authority is responsible for the recognition of the device and what are the requirements to seek compliance. (Ramakrishna et al., 2015).

The Guidance on legislation: Borderlines with medical devices (MHRA, 2015) emphasizes that not all equipment used by a health professional or present in the health area is considered a medical device. In general, to be a medical device, it must present a ‘medical purpose.’ The intention of the device, once in the market, will be displayed in the labeling, instructions, manuals and promotional material. (Regulation (EU) 2017/745)

Figure 4, in the next page, helps to illustrate a classic route that manufacturers need to trail to meet the medical device regulatory requirements. The course presents minor observations and cross-references to the regulation. The image is an adaptation of Figure 2.1 (Ramakrishna, Tian et al., 2015 p.33) and the compliance route of the "EU Medical Device Regulations - Challenges to research and startups” created by Petri Pommelin (2018).

It is followed by the explanation of essential points to claim compliance with the Medical Devices Regulation. The information given in the next sections are self-explanatory and does not follow a chronological order.

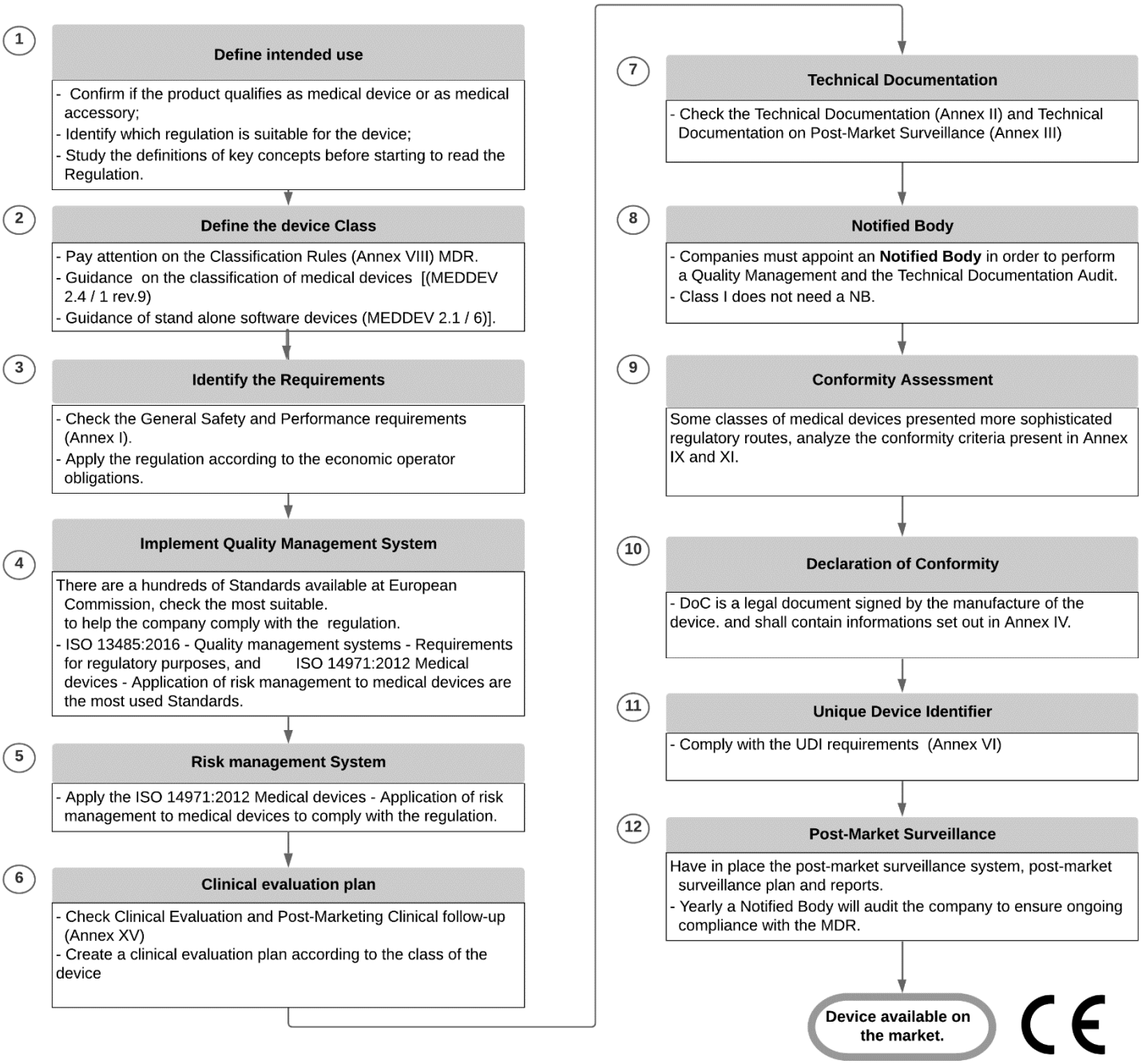

Figure 4 The route to comply with the regulatory requirements for a medical device manufacturer in the EU.

3.1 Defining, classifying and identifying: firsts steps to comply with the regulation

The new regulation takes seriously the risks concerning to place the medical device on the market or enable it into service. Article 5 of the regulation claim that to obtain the CE marking certification; companies must comply with European Commission Regulation. (Regulation (EU) 2017/745)

For manufacturers to achieve the performance intended and fulfill the safety and effective requirements proposed in Annex I of the Regulation, manufacturers cannot jeopardize the clinical condition or the safety of the users or patients. The general safety and performance requirements shall consider its intended purpose. Manufacturers must establish, implement and maintain a risk management system to demonstrate the conformity with the “General Safety and Performance Requirements” and must include a clinical evaluation (Regulation (EU) 2017/745).

One of the first septs, mentioned in figure 4, is to confirm if the product is as a medical device, classify it and identify which regulation is suitable for the device. To determine the classification manufacturers shall use the Annex VIII, “Classification Criteria” of MDR.

Once the device is qualified, the Company must appoint a Person Responsible for regulatory compliance (PRRC) as it will be described in section 3.3 of this thesis.

3.2 Routes of conformity for each class of device

The Conformity assessment procedures referred in Article 52, cited that manufacturers shall verify if they are following the conformity assessment procedures (Annexes IX and XI of the regulation). The routes to follow up will depend on the device class and consequently on the level of device risk.

The Member State may require access to the documents, such as the technical documentation, audits and others documentations relating to Article 52 of the Regulation, in an official Union language(s) (Regulation (EU) 2017/745)

The following flow chart briefly shows these conformity assessment routes according to each device classification. The Image is an adaptation of the Conformity Assessment Procedures created by Emergo (2018).

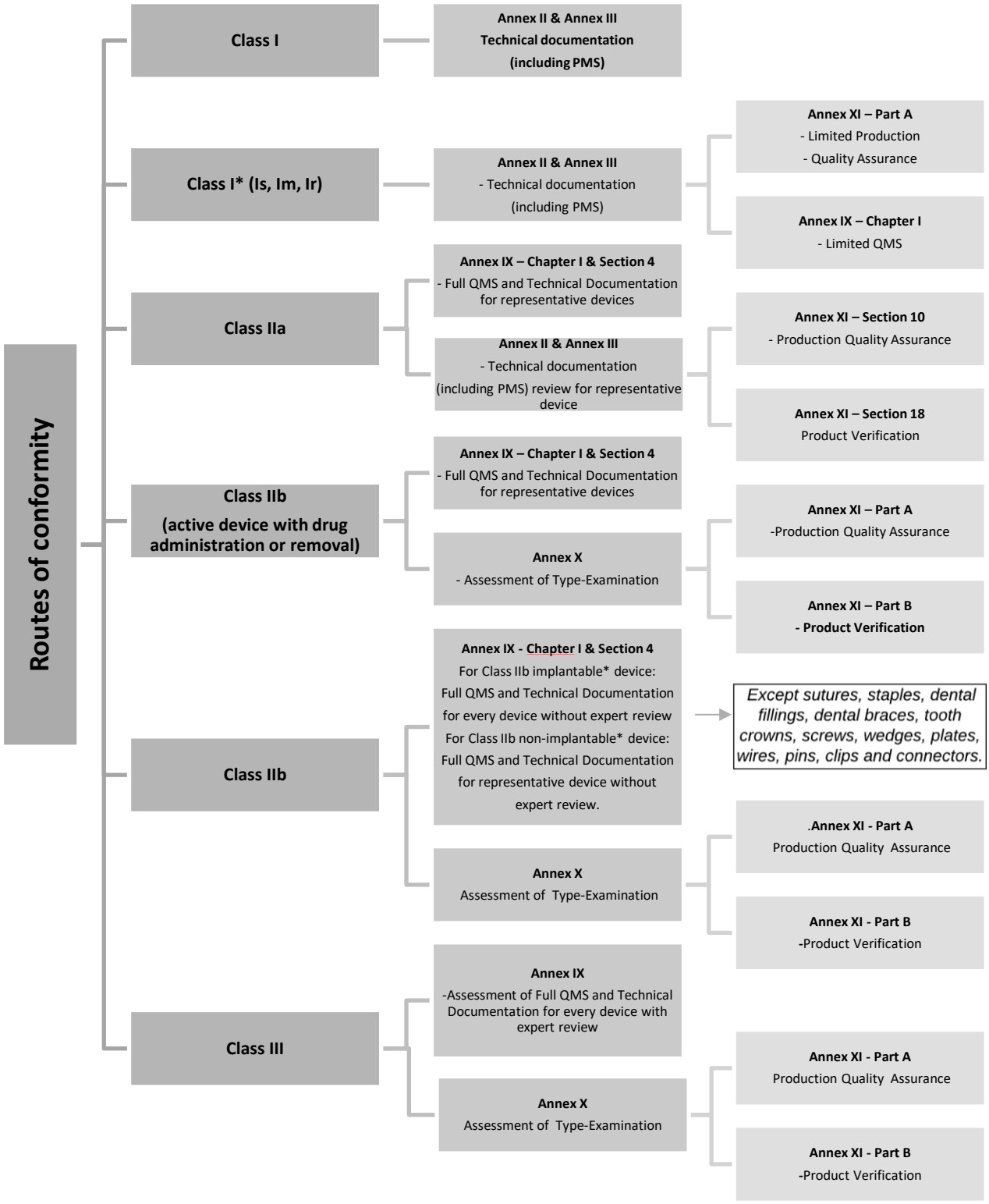

Figure 5 The flow chart illustrates these conformity assessment routes according to each device classification. Edited Emergo (2018)

3.3 General obligations of manufacturers

In the European market, and under the new regulation, manufacturers are required to take responsibility for obtaining the CE-mark of their products. They need to comply with the MDR by May 2020.

According to Article 10, manufacturers need to ensure that their devices were designed and manufactured in conformity with the Regulation. A continuous interactive process (Risk Management) shall be established, as described in Section 3 of Annex I. Additionally, manufacturers shall conduct a clinical evaluation under Article 61 and Annex XIV, including a post-market clinical follow-up (PMCF). Other requirements as Quality Management and Technical Documentation are needed to obtain the Declaration of Conformity (Regulation (EU) 2017/745).

Paragraph 16 of the article 10, says that once completed all these obligations and the requirement has been proved, manufacturers must to create the Declaration of Conformity mentioned in the article 19 of the regulation. This step will enable manufactures apply CE marking to their devices, according Article 20." (Regulation (EU) 2017/745).

3.4 Clinical Evaluation

Companies wishing to sell medical devices in Europe or in service must produce and maintain a Clinical Evaluation Report (CER) in accordance with the Regulation. However, before undertaking a clinical evaluation, the manufacturer should, therefore, define its scope based on the level of clinical evidence, which should be commensurate with the characteristics of the device and its purpose. Clinical Trial Reports (CER) are only required for Class I devices, while high-risk devices should be accompanied by robust clinical investigations (CI) (Regulation (EU) 2017/745).

For manufacturers who are preparing to implement clinical evaluation, the use of ISO 14155: 2011 on good clinical practice is an excellent tool to comply with the requirements of the regulation. Moreover, it should be in accordance with the latest version of the "Ethical Principles for Medical Research Involving Human Subjects by the World Medical Association (WMA) Declaration of Helsinki" mentioned in the Regulation. (Regulation (EU) 2017/745).

3.5 Eu Declaration of Conformity

Producing a Declaration is one of the necessary tasks involved in CE marking. The Declaration of Conformity (DOC) is a Legal document, which the manufacturer declares that their device follow the requirements present in the regulation. It is a simple process to generate a Declaration, which companies create and sign after they have compiled the Technical Documentation. (Regulation (EU) 2017/745)

The declaration is made after the manufacturers have followed all the steps shown in figure 4 and after the manufacturers have proved that their product meets the requirements of specified EU regulation, before releasing the product for sale. The manufacturers usually issue their Declaration of Conformity. However, high-risk devices manufacturers must select Notified Body (NB) to evaluate their devices to obtain a CE mark certification. (Regulation (EU) 2017/745)

Article 19 of the regulation state that " The manufacturer shall continuously update the EU Declaration of Conformity. Moreover, the DoC shall contain at least the information set out in Annex IV. The manufacturer is responsible for comply with the requirements of the regulation and with any other legislation relevant to the device." (Regulation (EU) 2017/745)

Once the device is on the market, the manufacturer should make accessible the product information, such as manufacturers, certificate issues, modifications, suspensions, withdrawals, refusals, and clinical investigations, and should be available from the European Medical Devices Database (Eudamed). Any adverse event must be reported to the Competent Authority (Venkatesh and Bandla 2017).

3.6 CE marking of conformity

Figure 6 CE marking

"CE" as illustrated on the top of this page, is the abbreviation of The CE marking. Paragraph 42 of Article 2 of the Regulation says that the "CE marking" present in the devices indicates that a manufacturer showed conformity with the requirements

presented on the Regulation and with other applicable standards. (Regulation (EU) 2017/745).

Manufacturers can affix the CE marking once they have signed a 'Declaration of Conformity.' Devices should have as a rule the CE marking following the requirements presented in Annex V of the Regulation. Except for custom-made or investigational devices. (Regulation (EU) 2017/745)

The CE marking implicates that CE-marked device may have free access to circulating around the European market, facilitating the exportation to other countries. However, medical devices are subject to inspection by the market surveillance authorities of the relevant member states, if necessary. (Regulation (EU) 2017/745)

3.7 Medical Device Nomenclature and Unique Device Identification (UDI)

To improve the monitoring of the security and performance of the devices available in Europe and to maintain transparency in the distribution chain, it was decided in April 2010 to create a database with high quality operational data stored in accordance with the specifications set out in the medical devices regulations, called the European Databank of Medical Devices (Eudamed) (Regulation (EU) 2017/745).

Eudamed is a platform developed by the European Commission in cooperation with the Member States. Eudamed aims to increase market surveillance by making available valuable information regarding the medical device, allowing the traceability of the medical device (Regulation (EU) 2017/745).

The release of the Eudamed system will allow a "massive amount of data which will be available to the European Authorities in the future" (EUMDR 2019). This database, according to EUMDR (2019) is one of the most significant changes adopted by the new European Union Medical Device Regulations. Moreover, the UDI system suits for most of the medical devices except custom-made devices (Regulation (EU) 2017/745).

Eudamed will be available in May 2020. This action will allow Europeans and others around the world to have access to crucial information from every medical device available on the European market. (Regulation (EU) 2017/745)

3.8 Post-market Surveillance

The medical device post-market surveillance (PMS) helps manufacturers to follow the production of the device once available on the market and generates constant feedback which allows manufacturers to keep a high standard of product quality and consumer satisfaction. It also reduces the susceptibility of occurring incidents through useful processes and procedures documentation. The PMS is an ongoing process of review and risk assessment throughout the life of the device. (Regulation (EU) 2017/745)

The regulation requires that for each medical device the manufacturer plans, establishes, documents and implements a PMS system efficiently as part of the Quality Management System, and its complexity must be proportional to the risk class of the device. Notified Bodies have to audit/check that there is a competent system in place. PMS systems are based on records received from the company through feedbacks, reports, literature reviews. (Regulation (EU) 2017/745)

Manufacturers of class II or higher shall provide a Periodic Safety Update Report (‘PSUR’) for each device summarizing the results and conclusions of the analyses of the PMS plan referred to in Article 84, throughout the lifetime of the device concerned. Manufacturers of class I, on the other hand, shall prepare a post-market surveillance report only when necessary. (Regulation (EU) 2017/745)

4 QUALITY MANAGEMENT SYSTEM

The majority of the medical device industry already have a Quality Management System (QMS). However, under the new MDR regulation most of the medical devices, whether currently certified to a European Medical Directive or yet to be certified, will need to acquire a QMS (Regulation (EU) 2017/745).

Quality Management System is a combination of processes and procedures that are specific to the manufacturer's products, organization, and structure. The QMS standards have two main functions— improving the effectiveness of goods and services and ensuring the authenticity of the product. QMS certification prevents fraudulent medical devices from entering the market. (Ramakrishna et al. 2015).

The requirements vary in different countries according to their different regulations. In Europe, it is common to use ISO 13485:2016 Medical devices - Quality management systems. It helps manufacturers to meet the compliance requirements of the EU regulations.

4.1 General requirements for Quality Management according to MDR

Manufacturers must play an active role during the documentation process, to guarantee that the production of the device continues to conform with the terms of the Regulation. (Regulation (EU) 2017/745)

The Quality Management System must embrace all the elements, parts or segments of the manufacturer's organization, and It shall oversee the structure, responsibilities, procedures, processes and management resources to achieve compliance with the Regulation (Regulation (EU) 2017/745).

As referred in the Regulation, the QMS shall address at least the aspects covered at the General obligations of manufacturers referred to in Article 10, following up these aspects listed in the Regulation:

- Responsibility
- resource and risk management
- clinical evaluation

- production realization
- verification of the UDI assignments
- post-market surveillance vigilance.

According to the Regulation, the person with overall responsibility for conducting audits of the manufacturer's quality management system shall have “proven qualifications in the relevant field, present appropriate knowledge of devices legislation as well as related harmonized standards” (Regulation (EU) 2017/745).

4.2 Harmonized Standards

Regulations and standards usually do not designate how to perform activities to seek compliance. The use of these standards, in fact, remains voluntary, which means that manufacturers, operators and other conformity assessment bodies are free to decide which strategies they will use to demonstrate compliance with mandatory legal requirements. This initiative allows them to produce their practices and procedures to meet their needs better (Roldán and Manuel 2016).

However, there is a list of mandatory requirements which must be included to comply with the Medical Device Regulation. The harmonized standards, developed by the recognized European Standards Organization, exists to support manufacturers reach compliance with relevant EU legislation. Although it may not be compulsory to follow these standards, companies that use it tend to comply with regulations more effectively (Roldán and Manuel 2016). Also, establishing this practice enables manufacturers to maintain the effectiveness of the company's operational processes, ensuring consistency and safety from the product design to the delivery of the medical devices. (Manz 2018)

There are many harmonized standards currently available in Europe, each of which lays down requirements for compliance in a given area, whether in the quality management, development of a process, or in risk management. The industrial area and its regulation will determine which standards to follow (Roldán and Manuel 2016). The following standards are some of the relevant harmonized standards for the medical device:

- ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes.
- ISO 14971:2012 - Application of risk management to medical devices.
- ISO 14155:2011 - Clinical investigation of medical devices for human subjects - Good clinical practice.
- IEC 62304:2006 - Medical Device Software - Software life cycle processes.

The first one, ISO 13485:2016, defines all the processes, roles, responsibilities and procedures in the company to achieve effective quality management (ISO, 2016).

The ISO 13485:2016 applies to companies regardless of the size and is a popular medical device standard used especially among manufacturers. Activities covered by the standards include design and development of the company, marketing, sales, production, storage and distribution, administrative roles and other associated activities. The ISO 13485:2016 does not limit to manufactures, suppliers or external parties that provide the medical product can also use the standard (ISO, 2016).

Application of risk management (ISO 14971:2012) applies to all stages of the medical device. The standard has been developed with precision for manufacturers of medical devices/systems to recognize the risks associated with medical devices. This standard also applies to IVD and aims to help manufacturers measure and evaluate the risks of their devices, minimizing risk and monitoring the effectiveness of the company in risk management. (BSI, 2012)

ISO 14155: 2011 complement risk management by address good clinical practice. The ISO 14155:2011 ensures the scientific conduct of clinical research and secure the credibility of results achieved in humans by define requirements to protect the rights, safety, and well-being of a human. (ISO, 2011).

The Medical Device Software standard (IEC 62304:2006) although have been in the market for a while provides a conceptual framework of life cycle processes for the safety issues, development, and maintenance of the medical software. Currently, a new version of this standard is under development, and It applies whether the software is a medical device or when the software is included in some medical device. Each software's life cycle processes are separated into a set of techniques and methods, covered by the standard. It ranges from product development and design architecture to maintenance process and risk management process (Roldán and Manuel 2016).

Usually, standards differ in their approach and degree of prescription. For that reason, standing alone may not cover all of the requirements mentioned in the MDR. Following more than one standard is a wise choice that some companies make to comply with the regulation. In overall, standards have many common requirements, and it is often more efficient to combine their approaches.

5 BENETE: CASE STUDY

The content present in this chapter is based on the information provided by the case company.

Benete Oy was initially founded as a management consulting firm by Kari Bäckman (CEO). After participating in a research project in 2014-2016, Benete decided to invest its resources in Life Analytics Platform. Since then, Benete has been developing projects in partnership with other public organizations and companies in the healthcare area.

The positive results carried out as a proof-of-concept in Finland, boosted Benete to set up user requirements to launch Life Analytics Platform in the Finnish Market. During the company trajectory, Benete has also started a co-development project with the city of Tampere on monitoring of patients with heart disease remotely.

Now, Benete is actively exploring opportunities for internationalization. According to the company, Denmark and the Netherlands are chosen as first case-study countries to develop a market entry strategy.

5.1 Company concept

Life expectancy and quality of life have been increasing steadily over the years as well as levels of diagnoses related to dementia. Not surprisingly, the lack of adequate caregivers and the rising costs of health care have created the need for innovative ways to provide more efficient care services.

Currently, the information on the individual functioning and the care needs are obtained through functional evaluations made during a medical consultation or by the nursing visit. In this context, the health system creates partial data, limiting its knowledge about the patient only when the patient gets in contact with the health professionals. This process makes the information incomplete because the perception of behavioral changes should be carried out routinely and continuously.

Another problem found in the current health system is that disorders commonly present in the elderly, such as disabilities or cognitive disorders, are often perceived as a slightly advanced level. In this situation, it may be challenging to decide whether to consider

increasing palliative care before transferring the elderly to a nursing home or sheltered accommodation.

The service, "Life Analytics Platform," is an upgradeable platform which recognizes the subtle changes in an individual's functioning abilities, transmitting valuable information concerning the physical and mental well-being of the elderly. The company aims, in the long term, to bring the data on individual functioning most conveniently and helpfully way to help in the early diagnosis and increase the effective treatment of various diseases, including cognitive disorders which are challenging to recognize until a more advanced stage.

5.2 Benete service “Life Analytics Platform.”

Benete’s software aims to support social- and healthcare providers with the information of senior’s condition. To re-design current care processes and to offer support in digitalization of the senior care processes. To promote better healthcare outcomes through better patient understanding.

Seniors and family members will benefit from an early diagnosis of cognitive decline. Once the symptoms progress, the software will support seniors’ daily life in a way that will empower them to maintain independence as well as enable health professionals and family members to follow the elderly actions to promote personalized care. Creating an environment where elderly can use and benefit from innovative technologies permitting a more active home life and less reliance on outside assistance.

5.3 Target group

Benete will offer their services to two groups of customers: elderly care providers in public and private sectors and seniors family members. The earning model of the company is based on software as a service (SaaS), where a customer pays a subscription fee monthly per individual user. Monthly fee includes production costs and the cost of sensor devices.

5.4 Benete’s software under the Medical Device Regulation

In the present circumstance, the Benete software is not qualified as a medical device. The platform performs limited storage, archiving, and will enable simple communication between software and the parts involved and according to the classification and qualification described in the (MEDDEV 2.1 / 6, 2016); (MHRA 2018) it is not considered a medical device because the platform does not perform an action on the acquired data.

The Benete’s initial idea is to generate information enabling a professional to make the clinical decision. However, being able to monitor and provide information that can be used to make decisions concerning diagnostics in seniors classifies the software as a medical device.

In this scenario, the software has a medical proposal, since it intends to indicate the risk of a specific patient developing a disease based on the data entered for that patient and intends to allow remote access to the information in the monitors, defining filtering rules for any alarms generated by the platform. (MEDDEV 2.1 / 6, 2016); (MHRA 2018); (Regulation (EU) 2017/745)

6 CROSS-REFERENCE WITH REGULATORY REQUIREMENTS: CASE STUDY

As stated earlier, the Benete software is not yet a medical device. However, as the company intends to use the software for medical purposes in the future, it is advisable to create an action plan to comply with the Regulation in advance.

Implementing the vision of becoming an active device, capable of diagnosing, monitor and analyze the information collected to produce accurate reports about the condition of the patients, demonstrates that the software has a medical purpose. Which according to rule 11, presented in the classification rules (Annex VIII) of the Regulation and as described in the MEDDEV 2.1 / 6 (2016) would be considered as a medical device class II.

This chapter will describe the following actions the case company would need to achieve once the software crosses the borderline and becomes a medical device. The chapter considered the intended medical purpose of the Life Analytics Platform mentioned in chapter 5, and the requirements set by the MDR, and relevant harmonized standards. The methods and actions proposed are expected to be applied by the company as guidance to develop and implement the company's strategies.

6.1 Defining the route to conformity

Through documentation reviews regarding the device classification (Regulation (EU) 2017/745); (MEDDEV 2.1 / 6 2016); (Emergo, 2018); (MHRA 2015) and through regular meetings made during the development of the thesis, with the CEO of the case company, it was concluded that the software would possibly be classified as Class IIa.

The classification was a necessary step to be able to determine which route the company should trail (figure 7) in order to understand the requirements and how to achieve conformity. However, it should be noted that accurate classification may vary according to the number of medical purposes. Whether the software will belong to Class IIa can only be elucidated when the company has defined the real intended purpose.

The diagram below shows the compliance route considering classes IIa and IIb. The image is based on the Europe CE Marking Regulatory Process for Medical Devices by Emergo (2018) and shows the main steps to achieve compliance with the new regulation. Each step will be explained in more detail in the following sections.

As Benete software will become a medical device in the coming years, it is still advisable to take all the decisions regarding the development of the stand-alone software and the company's activities according to the Medical Device Regulation. The company should identify and evaluate the applicable regulations based on the type of software, the level of risk and the intended purpose. If the purpose of the software has one or more objectives displayed in the description of the medical device (located in section 2.1 of this thesis), the classification of the device must follow the rules applied in the highest classification of risk (Regulation (EU) 2017/745).

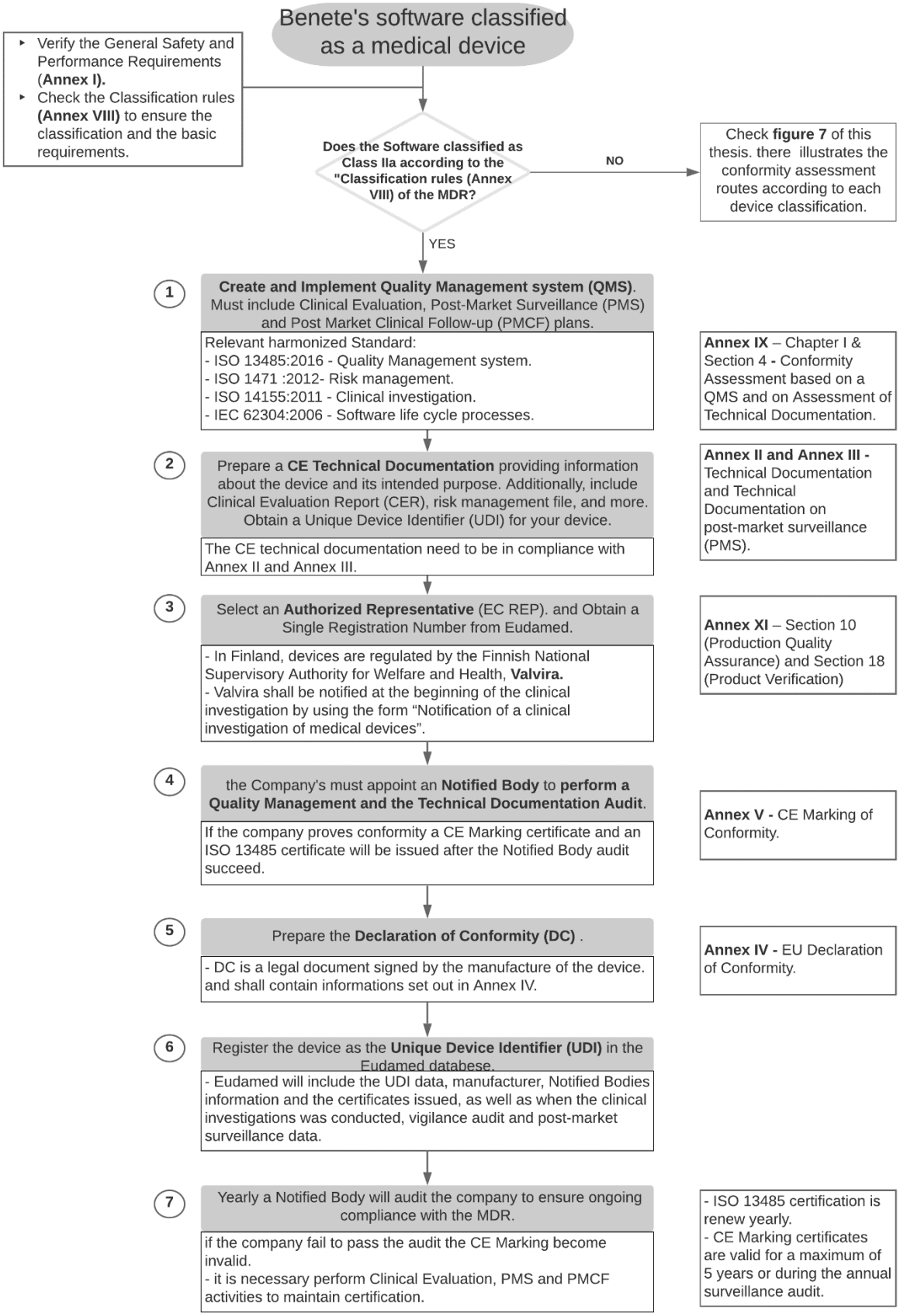

Figure 7 Benete´s Regulatory route to achieve compliance with the Medical Device Regulation.

6.2 Creating and Implementing the Quality Management System

The creation and implementation of the Quality Management System (QMS), presented in the diagram (figure 7), is one of the crucial steps to comply with the Regulation. In fact, the benefit of having a QMS are numerous, regardless of the device classification and company type or size as referred in chapter 4.

The core of quality management guides companies towards improved performance, and it should be maintained as a high priority step by the case company.

One of the implementation phases is to get management support. The company should consider creating and implementing QMS as a long-term project, and the manager should decide whether the company will use external consultants or whether it will use pre-established document templates with a "Do-It-Yourself approach." (Advisera 2017)

The image below (figure 8) highlights the pros and cons of each type of approach previously mentioned helping the company to choose the method that best suits their needs. The picture is based on the white paper created by Advisera (2017) where it contrasts the implementation of QMS done by a consultant versus by the company itself.

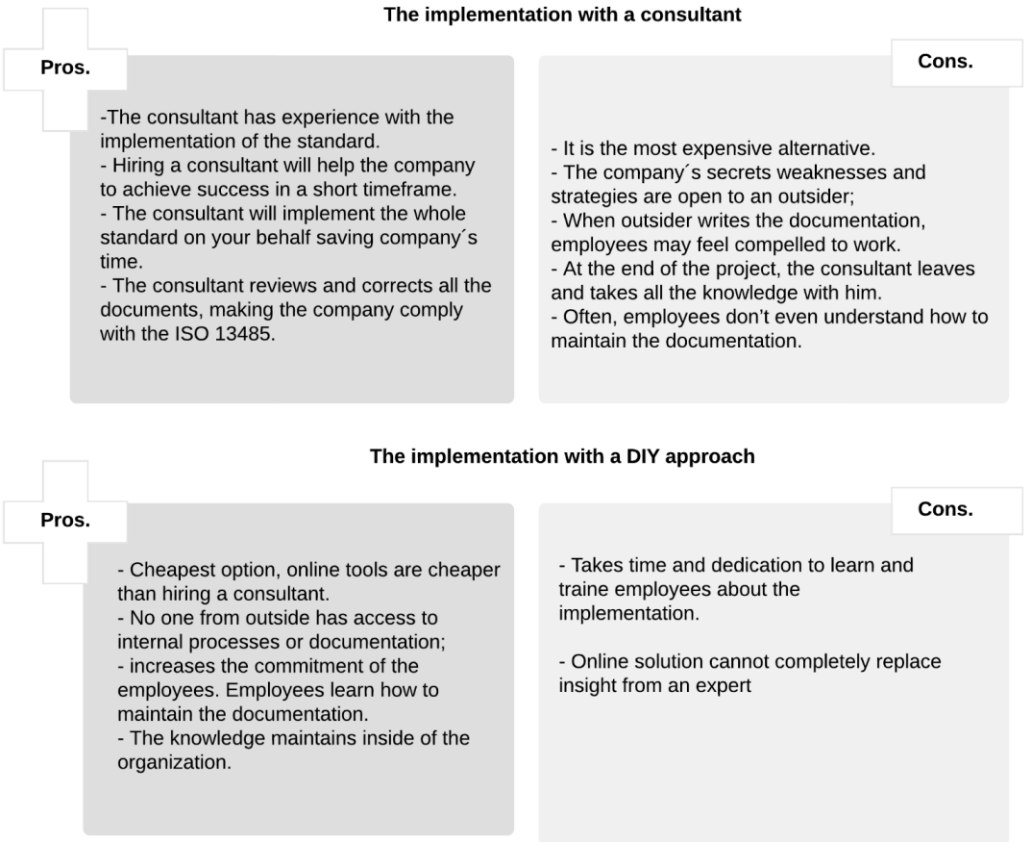

Figure 8 Pros and cons of implementing a Quality Management System with a consultant vs self-approach.

For a small company, with its limited resources, it is an advisable alternative to choose to write its documentation if the time is not an issue. Besides being a more practical choice, it still reinforces the commitment of the employees and their knowledge on the subject. (Advisera 2017)

The Managing Director should define the project manager, milestones, deadlines, and determine who will be responsible for approving policies, procedures. The company's Managing Director is also responsible for the development of quality policy, objectives, project-specific plans and the management review of the QMS results, such as the QMS internal audits to ensure the effectiveness of the QMS. (IMDRF/SaMD WG/N23 2015).

The QMS processes and procedures should be explicitly tailored to the needs of the company and should be built and managed around methods which support the software lifecycle activities. The company must provide the appropriate level of resources (people, tools, training, e.g.). Such infrastructure is used to support the development, production, and maintenance of the product, to identify the applicable legal requirements and to

ensure the success of the processes and activities of the product life cycle according to the regulation and ISO requirements (IMDRF/SaMD WG/N23 2015).

Defining the scope of the QMS, management commitment and responsibilities should be the next step. In this phase, the company should focus on writing the Quality policy. The top management needs to ensure that the quality policy meets the company's purpose, Including a framework for establishing and evaluating quality objectives, to comply with obligations and to keep the effectiveness of the QMS. As part of the process, the manager needs to communicate and demonstrate to the company the importance of the quality policy by mentioning it during employee meetings, in business reports, and other communications channels (Manz, 2018).

The book "Systems of Quality Management of Medical Devices: Strategy and Techniques for Improving Efficiency and Effectiveness" (Manz, 2018) explains the concept of "establishing and maintaining" through the phrase:

"Say what you do, do what you say and prove it! "

"Say what you do." The book refers to policies, procedures and works instructions which the company must have, so Manz (2018) documents should be well drafted, clear and concise. The company should write the documentation in such a way that the language can be understood by all employees and must keep it in a place that is always available for use.

"Do What You Say," Manz (2018) emphasized the importance of including a training program for employees. For Manz (2018), a good training program aligned with the quality objectives of the company and the personal development of the employee is a powerful tool to avoid problems of quality and compliance.

The *"Prove It"* concept requires good documentation practices (GDP) (Manz, 2018). Records are used to provide evidence of the results obtained or to document the activities performed. These records are generated to demonstrate compliance with the QMS. They must be appropriately identified, stored, protected and preserved for a specified period. For the case company, the proper management of the QMS requires that the responsible person review and approve the documents before using them; and ensure that the current versions of the documents are always available for use. Currently, records can be kept in the traditional way, printed, or electronic format (IMDRF/SaMD WG/N23 2015).

The purchase of the ISO 13485: 2016 Quality Management System is one of the instructions given as a strategy to facilitate the creation and implementation of the QMS for the case company. The activities covered by the standard previously mentioned in section 4.2 of the thesis, and it includes processes which are necessary for the product life cycle of the medical product, such as product development requirements, manufacturing transfer requirements, release to market requirements and post-market activities requirements (Manz, 2018).

Another recommendation is the incorporation of ISO 14971: 2012, risk management. This standard is designed to comply with ISO 13485, the norm intended to support the company understand and create measures to evaluate the risks of the device while minimizing the hazards situations.

6.3 Prepare CE technical documentation

This phase is best visualized in image 5 of this thesis. The image showed the steps that the manufacturer needs to follow to comply with the regulation of the medical device. After you implement QMS and Risk Management, the company must create a Clinical evaluation plan. This is another essential step in acquiring the necessary documentation for the CE mark.

Clinical evaluation is a systematic process and is planned to be generated continuously. Collecting, analyzing and evaluating clinical data is part of the process and should be an iterative as part of the QMS for medical devices. The quality and comprehensiveness of clinical evaluation should be tailored to the specific SaMD and intended use (IMDRF/SaMD WG/N41 2017).

According to the Software as a Medical Device (SaMD): Clinical Evaluation (IMDRF/SaMD WG/N41 2017), there are three types of clinical assessment which the case company should consider:

1. **Valid clinical association:** verifies if the association between the device output and how the clinical condition exams are supported by evidence.

This confirmation can be supported by existing evidence, such as bibliographic research, clinical research, professional society guidelines or new evidence, such as secondary data analysis or clinical trials.

2. **Analytical validation:** refers to whether the medical device meets the technical needs.

It is essential that the present company evidence shows that the SaMD has performed as expected. This indication can be generated during QMS verification and validation activities, life cycle software, or by producing new evidence through the application of databases or use of previous data.

3. **Clinical validation:** is based on the relevance of the clinical outcome of the device. For the company to succeed, it is necessary that the SaMD has been tested in its target population and by its intended use; and that users can achieve clinically significant outcomes through predictable and reliable use.

As the Analytical Validation, the clinical validation uses the verification and validation activities performed in the QMS to generate evidence. In addition, it is utilized existing data sources from studies conducted with the same intended use.

If the company cannot generate evidence to demonstrate any of the clinical evaluation described above, the company may change its intended use to one that may be supported by the available evidence or make changes to the software (IMDRF/SaMD WG/N41 2017). To help comply with regulatory requirements regarding the clinical evaluation, the Regulation recommends that manufacturers implement ISO 14155: 2011 referred in chapter 3.

Once this step has been completed, the company can move forward to prepare for compliance with the MDR.

The technical documentation, referred in figure 7, shall support the elements presented in the Annexes II and III of the Regulation such as:

Device's Information and specification as well as a reference to previous device design and, if applicable, similar generations of the invention; Information provided by the company regarding the labels, instructions, and symbols used; Complete information regarding the design and manufacturing processes and their validation; Proof of conformity with general requirements, present in Annex I of the Regulation; Risk management information and risk-benefit determination; Product verification and validation information, including detailed information on the pre-clinical and clinical data; Post-market surveillance plan drawn up following Article 84 and the EU declaration of conformity information as stated in the Medical Device Regulation.

6.4 Authorized Representative

In Finland, the devices are regulated by the Finnish National Authority for Wellness and Health, Valvira. It means that manufacturers domiciled in Finland must communicate their contact details and product information to Valvira. (WHO, 2017)

However, as a company is actively exploring internationalization opportunities, the responsible authorities in the other countries of interest of the company were highlighted below.

In Denmark, the Danish Medicines Agency is responsible for the regulation of medical devices and pharmaceuticals under the Danish Ministry of Health and Prevention. (WHO, 2017)

In the Netherlands, the national regulatory authority is the Dutch Healthcare Inspectorate. (WHO, 2017)

6.5 Notified Body

The definition of the Notified Body (NB) highlighted in the Medical Devices Classification, section 2.3 of this dissertation. For the European Union, the responsibility is to help manufacturers meet the safety requirements of the regulations. Also, according to the regulation, Class IIa, Class IIb, and Class III devices, the involvement of the notified body is compulsory.

This means that even if the company has chosen to build and develop the Quality Management System without the help of a Notified Body, the presence of the Notified Body is required in subsequent steps to perform an audit in the QMS and the Technical Documentation, certifying that the manufacturer complies with the Regulations. If the company proves conformity, the ISO 13485: 2012 certification is issued, and the company can prepare the declaration of conformity, mentioned in chapter 3, section 3.3 of these.

According to global medical device compliance consult, Emergo (2017), the estimated costs to obtain MDR compliance, is around $ 15,000 to $ 30,000 for a class IIa medical device. The estimated costs made by the company were based on the: “registration application fees, product testing, country representation, submission preparation

consulting and translation of documents, excluding the cost of implementing and auditing a quality management system". And the time required to get approval is between 3-5 months (Emergo 2017).

6.6 Prepare the Declaration of Conformity (DoC)

The Declaration of Conformity was described in chapter 3, section 3.3 of these. In general, DoC is no longer than one page, and according to Annex IV of the regulation, the declaration should contain the following information:

- Name registered, trading name or registered trademark, if applicable, its authorized representative and their information.
- Manufacturer draw up a statement that the DoC is issued under the responsibility of the manufacturer and that it follows the new Regulation.
- Include basic information of the UDI-DI as cited in Annex VI (Part C);
- Product information such trade name, product code. The information shall provide identification and traceability, as well as its intended purpose.
- State the risk class of the device in accordance with the classification rules (Annex VIII);

(Regulation (EU) 2017/745)

To enclose the document should include date and place of issue of the declaration, and the information of the person who signed it. An Example Declaration of Conformity has been added as an annex, can be found in Appendix 1.

6.7 Unique Device Identification

According to Article 33 of the new Regulation, the Unique Device Identification (UDI) data includes all the business operator's information related to the devices, and shall include also the Notified Bodies information, and any certificate issued. Data on clinical investigation must be available, as well as the vigilance and post-market surveillance data. (EUMDR 2019) The case company, as well as other economic operators, must contribute with the data input as mentioned in section 3.7.

6.8 Post-market surveillance (PMS)

As explained in section 3.8, the PMS helps manufacturers to generate constant feedback which allows manufacturers to keep a high standard of product quality and consumer satisfaction and It also reduces the susceptibility of occurring incidents. (Regulation (EU) 2017/745)

The case company shall plan, establish, and implements a PMS system efficiently as part of the Quality Management System, and its complexity must be proportional to the risk class of the company's device. (Regulation (EU) 2017/745). Additionally, the company shall provide a Periodic Safety Update Report ('PSUR') for each device summarizing the results of the analyses of the PMS plan. (Regulation (EU) 2017/745)

7 CONCLUSION

The present chapter outlines the intended purpose of this thesis, its limitations, and the outcome.

The thesis tried to answer the difficulties of the case company, which was to understand the requirements to comply with the Medical Devices Regulation and which are the steps the case company would need to follow once the software crosses the borderline and becomes a medical device.

The methods and actions proposed are expected to be applied by the company as guidance to develop and implement the company's strategies.

To answer the question, key concepts were introduced, such as: the definition of a medical device; the description of the software as a medical device, including the explanation of an active device and its rules, in order to understand what class the device of the company will belong, when the platform has a medical purpose, described in chapter 2. The regulation says that any device whose primary function is to monitor, diagnose, treat or prevent a medical condition is considered a medical device (Roldán and Manuel 2016). Therefore, it must comply with the relevant regulations present in the Regulation. Chapter 2 closes discussing the changes made in this new Regulation, highlighting the transitional period to comply with the new rules and allowing the companies to plan when they renew the technical documentation and processes to meet the new requirements.

The thesis continues with Chapters 3 and 4, outlining essential concepts to create a route to conformity; it shows that no route can be applied generally. The compliance route is influenced not only by the class of devices but also depends on the 'economic operator.' The economic operator, in this thesis, is the manufacturer and all subsequent steps were directed to its responsibility.

Thereafter, relevant information about the company's case was presented. The company, Benete Oy, is developing a platform which will bring improvements in the way professionals and families deal with care for the elderly.

The software, Life Analytics Platform, is an innovative service which will bring more accurate information about the daily life of the elderly to enable them to maintain

independence and allow health professionals and family members to follow the most appropriate actions to promote personalized service. As discussed in Chapter 5.

The literary reviews of the Medical Devices Regulation highlighted in Chapters 3 and 4; the presentation of the company and its objectives mentioned in Chapter 5; and the support received by the CEO of the company during regular meetings, served as inputs for the development of the action plan. The route to conformity was designed by taking into account the company's situation.

Although Benete's software is not yet a medical device, the company plans to make its platform a medical device in the near future. Therefore, it was suggested to create a plan of action that covers the regulations present in the MDR in advance. Figure 7 was the regulatory route suggested to the case company for compliance with the regulation of medical devices of class IIa. The company should also use as a complementary route the figure 4, present at the beginning of the thesis.

The classification was a necessary step in determining which route the company should follow. However, the actual classification can only be confirmed when the company provides evidence that the device displays the intended purpose expected. As suggested in Chapter 6, the company will need to test its device on its target population, seniors, with the intended use; If the company cannot generate evidence to demonstrate its intended purpose, the company may change the intended use of the device. (IMDRF / SaMD WG / N41 2017) However, it may affect the classification of the device and the compliance route described in the thesis.

The European Standards Organization develops standards to help companies demonstrate compliance with relevant EU international legislation (European Commission 2016). The International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) have published several harmonized standards to assist manufacturers of medical devices in complying with the Regulation (Roldán and Manuel 2016).

For the case company, it was initially suggested to purchase the ISO 13485: 2016 Quality Management System, as a strategy to facilitate the creation and implementation of the QMS. The QMS guides companies to improve the effectiveness of products and services and is an essential requirement to compile with the Regulation.

The QMS operates as a support for the other requirements. Another recommendation was the incorporation of ISO 14971: 2012, Application of risk management. This standard was designed to comply with ISO 13485, and it supports the company to measure and evaluate the risks of the device to minimize hazardous situations. (BSI, 2012) In addition, the Regulation, recommend the use of ISO 14155: 2011 to help manufacturers to comply with good clinical practice, ensuring the credibility of the results achieved in humans. (ISO, 2011).

After implementing the QMS, risk management and run a clinical evaluation plan, the company can move forward to prepare the technical documentation, referred in chapter 6 of the thesis. That documentation must be audited by a Notified Body, which has the responsibility to help manufacturers to comply with regulation safety requirements.

Only after confirmation of these documents can the company declare compliance through the Declaration of Conformity, and thus receive the "CE marking," the seal of conformity with the regularization.

7.1 Thesis limitation and future research

This thesis was designed for a new company and tried to address the essential aspects of regularization for a stand-alone software manufacturer. Although the thesis addresses almost every aspect of the new Regulation, it is necessary to consider that each has its particularity. Therefore before taking any action, it is crucial to define and classify the type of device and the economic operator before identifying the route to compliance. For the company in the case, the route of compliance was based on devices class IIa. However, if the company changes its purpose, the software classification and compliance rout may change.

But the limitation which by far was the most intriguing was the lack of bibliographical references, documents, and guidance under the new Medical Device Regulation. Most of the documents are under the current Directives. All the guidance and other support materials need to be reviewed in the next few years to comply with the new Regulations, as well as some standards which also need to be revised to comply with the new requirements mandated by the new Regulations.

There is a wide range of possibilities for future research in this area, such as:

- applying the same idea used in this thesis to help others start-up companies to comply with the medical device regulation using different classes and types of medical devices (non-invasive devices, invasive devices, in vitro devices, e.g.);
- or develop a more detailed plan to help companies understand and conduct risk management and clinical evaluation;
- or even help companies develop efficient software lifecycle by considering the new regularization and the company situation.

However, it would be quite interesting to consider as future research, "the relationship between harmonized standards, such as ISO 13485, ISO 14155, ISO 14971 with the new Medical Device Regulation", analyzing whether there are gaps between the new regulation and the currently available ISOs.

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Example of the EU declaration of conformity (DoC) adopted by Conformance (n.d.).

EU Declaration of Conformity (No. 18D9999)

In accordance with of European Parliament and Council Decision No 768/2008/EC Annex III

1. *Product model / product:*

Product	Widget manufacturing machine
Model/type	Super 77
Serial nos.	00120 - 01000

2. *Manufacturer*

Manufacturer	Acme Widget Ltd
Address	Unit 1, Wall Farm, Ind. Est., Walsall, W. Midlands, B1 23B

This declaration is issued under the sole responsibility of the manufacturer

3. *This declaration is issued under the sole responsibility of the manufacturer.*
4. *Object of the declaration:*

Product	Machine for manufacturing widgets with a bifurcated sprocket
Throughput	77 widgets/hour
Max. Temperature	200°C

5. *The object of the declaration described above is in conformity with the relevant Union harmonisation legislation:*

2006/42/EC	The Machinery Directive
2014/30/EU	The Electromagnetic Compatibility Directive
2011/65/EU	The Restriction of Hazardous Substances Directive

6. *References to the relevant harmonised standards used or references to the other technical specifications in relation to which conformity is declared:*

Reference & Date	**Title**
EN ISO 12100:2010	*Safety of machinery. General principles for design. Risk assessment and risk reduction*
EN 746-1:1997 + A1:2009	*Industrial thermoprocessing equipment. Common safety requirements for industrial thermoprocessing equipment*
EN 61000-6-1:2007	*Electromagnetic compatibility (EMC). Generic standards. Immunity for residential, commercial and light-industrial environments*
EN 61000-6-3:2007 + A1:2011	*Electromagnetic compatibility (EMC). Generic standards. Emission standard for residential, commercial and light-industrial environments*

7. *The technical file is available from the manufacturer at the address above*

Signed for and on behalf of:	Acme Widget Ltd
Place of issue:	Walsall
Date of issue:	20th April 2016
Name:	Nigel Watkins
Position:	Technical Director
Signature: