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Medical software certification processes in Europe, USA and Brazil

Biomedical Engineering Integrated Masters Dissertation in the field of Biomedical Instrumentation and Biomaterials presented in the Department of Physics of the Faculty of Sciences and Technology of the University of Coimbra

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Medical software certification processes in Europe, USA and Brazil

Dissertation presented to the University of Coimbra to complete the necessary requirements to obtain the degree of Master in Biomedical Engineering

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Abstract

Nowadays medical software is a continuously growing market. It is essential for the manufacturers of this type of medical product to follow mandatory regulatory requirements and implement the necessary measures in the company in order to market their product in different countries.

The medical product to be certified is OneCare Sensing marketed by ISA, a monitoring software solution intended to collect, store, display, transmit and provide alerts of physiological parameters such as temperature, blood glucose and pressure and pulse oximetry of users at home allowing distance monitoring by family or clinicians, reducing journeys to healthcare facilities or domiciliary medical visits.

The aim of this thesis is to collect and analyze the regulatory requirements of this medical software in Europe, Brazil and USA. Regarding Europe a more pratical work was made by implementing in the company all the necessary requirements in order to obtain CE marking following the Medical Devices Directive 93/42/EEC. In the USA it is necessary FDA clearance by filling a 510(k) submission and implement a quality management system according to FDA QSR – 21CFR Part 820. Concerning Brazil, the regulatory agency is ANVISA and the submission type for this device is a *registro*. Also a quality management system according to the GBMP must be implemented within the company.

It was found that these regions despite having independent regulatory requirements they share some similarities. This study allowed the product to be one step closer to be marketed in Europe, Brazil and USA.

Keywords: medical software, medical device, certification process, CE marking, directive 93/42/EEC, FDA clearance, registro ANVISA, regulatory requirements in Europe, USA and Brazil.

Resumo

Actualmente o software médico é um mercado em crescimento contínuo. É essencial para um fabricante deste tipo de produto médico seguir os requisitos regulamentares obrigatórios e implementar as medidas necessárias na empresa para poder comercializar o seu produto em países diferentes.

O produto médico a ser certificado é o OneCare Sensing comercializado pela ISA-Intellicare, uma solução de software de monitorização destinado a recolher, armazenar, visualizar, transmitir e fornecer alertas de parâmetros fisiológicos como temperatura, níveis de glucose e pressão sanguínea e oximetria de pulso dos utilizadores em sua casa permitindo a monitorização à distancia de familiares ou clínicos, reduzindo as suas deslocações a estabelecimentos de saúde ou visitas médicas familiares.

O objectivo desta tese é recolher e analisar os requesitos regulamentares deste software médico na Europa, Brazil e EUA. Relativamente à Europa foi realizado um trabalho mais prático implementando na empresa todos os requisitos necessários para obter marcação CE seguindo a Directiva Médica 93/42/EEC. Nos EUA é necessária a autorização da FDA preenchendo uma submissão 510(k) e implementando um sistema de gestão de qualidade de acordo com FDA QSR – 21CFR Parte 820. Relativamente ao Brasil, a agência reguladora é a ANVISA e o tipo de submissão para este dispositivo é o registro. Tambem é necessário implementar um sistema de gestão de qualidade de acordo com GBMP na empresa.

Foi descoberto que estas regiões apesar de possuirem requisitos regulatórios independentes possuem algumas semelhanças entre si. Este estudo permite que o produto em questão fique um passo mais próximo de ser comercializado na Europa, Brazil e EUA.

Palavras-chave: software médico, dispositivo médico, processo de certificação, marcação CE, directiva 93/42/EEC, autorização da FDA, registro ANVISA, requisitos regulamentares na Europa, EUA e Brasil.

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Notation and glossary

AFE – Autorização de Funcionamento da Empresa

ANVISA – Agência Nacional de Vigilância Sanitária

BGMP – Brazilian Good Manufacturing Practices

BRIC – Brazil, Russia, India and China

CBPFC – *Certificado de Boas Práticas de Fabricação e Controle*

CFR – Code of Federal Regulations

CHF – Chronic Heart Failure

COPD – Chronic obstructive pulmonary disease

CGMP – Current good manufacturing practice

CVD - Cardiovascular disease

EC – European Comission

ECG - Electrocardiography

EEA – European Economic Area

EU – European Union

FDA – Food and Drug Administration

GHTF – Global Harmonization Task Force

HCO – Co-ordination activities

ICT – Information and Communications Technology

IEC – International Electrotechnical Commission

ISO – International Standard Organization

JRC – Joint Research Center

LF – *Licença de Funcionamento local*

MD – Medical device

MDD – Medical Devices Directive

MEDDEV – Guides to medical devices directives in the European Union

NB-MED – Co-ordination of Notified Bodies Medical Devices

PHC – Personalizing Health Care

PMA – Premarket Approval

QSR – Quality System Regulation

RMT – Remote Monitoring Treatment

SE – Substantially Equivalent

SIMPHS – Strategic Intelligence Monitor on Personal Health Systems

UK – United Kingdom

UNIAP – *Unidade de Atendimento e Protocolo*

USA – United States of America

VISA – *Vigilância Sanitária Local*

Table of Contents

1 Introduction

1.1 Framework

Nowadays the demand of more and better regulatory frameworks ensure that the medical products entering the market are safe and effective. The two main challenges for companies of these type of products are research and development along with keeping up with the updates on regulatory requirements and implement them in the company [1].

Manufacturers of medical devices need to adjust their regulatory framework for the countries where their products are sold. If they fail to do this a lot of capital could be lost by delaying the marketing of their devices. These regulatory requirements include things such as laws, standards, quality systems and product classification and registration [2].

In Europe, USA and Brazil there are some similarities in the regulatory process for medical devices. All systems have a definition of medical device and a risk based classification. This classification is a very important step since it dictates how to apply the correct regulations and quality systems [2].

In Europe the quality system is presented in the Medical Devices Directive and applied following the standards such as ISO 13485:2003, in the USA it is dictated by the FDA QSR 21 CFR Part 820 and in Brazil the Brazilian Good Manufacturing Practices. Despite their differences they share a lot of characteristics and usually if you already have one of these quality systems implemented it is fairly easy to comply with another one. Other specific requirements for each country will be addressed further in this document.

1.2 Objectives

The main objective of this project is to prepare the company regarding all regulatory requirements to posteriorly obtain CE marking on the product.

In order to achive this, a study of the OneCare Sensing was made. After, the medical device directive 93/42/EEC as carefully analyzed. In the course of this analyzis several norms where selected and ISO 13485:2003 was analyzed and ISO 14971:2007 implemented in the organization.

During the course of the work it was also verified that it would be important to identify the regulatory requirements for Brazil and USA in order to market the product in those regions in the future. This was a very general and

theoretical work but nevertheless essential to understand what to be done to comply with the legal requirements.

1.3 Thesis organization

This thesis is divided in 9 chapters.

In this chapter the theme, objectives and organization of the document are presented in order to provide an introductory framework of the project for the reader.

Chapter 2 is about project management. The company ISA-Intellicare is presented, the project contribution and the initial and final scheduling of the work are given.

Chapter 3 describes the medical product being studied. This includes the intended use, a small reference of the technology and the physiological signals acquired by the product related with pathologies that can be managed and/or avoided using OneCare Sensing.

Chapter 4 provides the state of the art. An introduction and market overview is given. Then the players of medical devices, the current EU funded program, market products similar to OneCare Sensing and the difficulties and barriers in the market are presented.

Chapter 5 is probably the most important chapter in the document. It describes in detail the medical device certification process in Europe and the work made during the project.

Chapter 6 mentions all the relevant normative framework which is applied to OneCare Sensing and compares two important standards, ISO 9001:2008 and ISO 13485:2003.

Chapter 7 describes the USA regulatory process for medical devices. In a way it tends to be more specific to medical software but doing that in a very thorough way was outside the scope of this work.

Chapter 8 outlines the Brazilian regulatory process for medical devices in a similar structure and function of chapter 6.

Chapter 9 provides the conclusion of this thesis. Future work that needs to be done in order to most effectively market the product in these three regions is presented. It ends with a brief summary of the project.

2 Project management

2.1 ISA – Intellicare

ISA-IntelliCare is a provider of products and services in the field of Remote Monitoring of Vital Signs and Ambient Assisted Living located at Rua Pedro Nunes, Building D, 3030-199, Coimbra, Portugal[3].

ISA IntelliCare is a spin-off of ISA. ISA – Intelligent Sensing Anywhere is a technology-based company with an experience of over 20 years in Machine to Machine (M2M) ' ready-to-go' , solutions, from software and hardware, development to the provision of services. It is a company specialized in two business areas – ISA Energy and ISA Oil & Gas – that offer and implement solutions and innovative services aiming toward efficiency and processes improvement in the energy, environment, gas and other fuels areas[4].

ISA IntelliCare mission is to offer high value added products and services for the global health market, by gathering relevant data about health and well-being status of the people, real time processing of data, regardless of distance and converting it in useful information and knowledge [3].

2.2 Project contribution

This project allowed to find and establish requirements necessary to obtain CE marking in a medical software necessary for its marketing in the European market. It also provides the legal framework in order to market medical software in USA and Brazil.

Part of the requirements analyzed are compiling a technical file according with the MDD which contains all the details about the product and implement a quality system specific for medical devices according ISO 13485:2003 – Medical devices – Quality management systems – Requirements for regulatory purposes.

In this way the project is perfectly aligned with ISA-Intellicare objectives and it can also provide help for manufacturers of medical software that need information in how to comply with legal requirements in Europe, USA and Brazil.

2.3 Scheduling the project

In the first phase of the project, essential tasks identified and planed. This was done to comply with the internship objectives in the most effective way but during work the schedule was adapted.

2.3.1 Initial scheduling

In the initial project proposition the following tasks and planning where identified. This is showed below in a Gant diagram.

Table 1 - Gant diagram: initial scheduling.

Cronogram											
Planning	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	Phase description
Phase I											Familiarization with ISA's working mode
Phase II											Study the equipment OneCare
Phase III											Study the applicability of the Directive 93/42/EEC to OneCare and compile a technical file
Phase IV											Studying ISO 13485:2003 and define processes to ensure compliance with this standard
Phase V											Notified Body communication to receive certification
Phase VI											Writing and present Master's thesis

2.3.2 Final scheduling

In the course of the project it was found that some tasks needed more time to be completed. Also it was agreed with the supervisor that Phase V should be substituted by "providing legal framework on medical devices marketing in Brazil and USA". Below is presented a Gant diagram on the final Scheduling of the project.

Table 2 - Gant diagram: final scheduling.

Cronogram											
Planning	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	Phase description
Phase I											Familiarization with ISA's working mode
Phase II											Study the equipment OneCare
Phase III											Study the applicability of the Directive 93/42/EEC to OneCare and compile a technical file

Cronogram											
Planning	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**Phase description**
Phase IV											Studying ISO 13485:2003 and define processes to ensure compliance with this standard
Phase V											Legal framework for medical devices in USA and Brazil
Phase VI											Writing and present Master's thesis

3 Product description

3.1 Intended use

This is the first step in order to obtain medical device certification in Europe. It's necessary to define an intended use for the medical device.

OneCare Sensing is a monitoring software solution intended to collect, store, display and transmit physiological measurements of users at home allowing distance monitoring by family or clinicians, reducing journeys to healthcare facilities or domiciliary medical visits [5].

Implemented in a tablet it collects, stores and displays physiological data captured in commercially available medical devices. It allows the transmission of the data to a remote secure server and storage in a database. Then the data can be available for consultation in the web by the user and clinicians for analysis and intervention. The medical devices that can be connected to the tablet are a glucose meter, weight scale, pulse oximeter, blood pressure monitor and thermometer. All of these sensors have CE marking according to the respective medical devices directives. One version of the software provides only real-time monitoring and the other does the same and emergency monitoring emitting alerts.

3.2 Telemedicine

Telemedicine or telehealth is defined by the American Telemedicine Association [6] as " the use of medical information exchanged from one site to another via electronic communications to improve patients' health status" . It could also be more generally defined as electronic communication technologies to provide health care at a distance [7]. Basically it refers to remote care monitoring and delivery that occurs outside clinical environment and usually in the patients' residence.

The percentage of adults over 65 years of age is increasing rapidly and with this healthcare costs are escalating beyond the ability of these older adults to pay for services [8]. To achieve the goal of improving the quality of elderly care it is essential to provide timely information and tools to care providers that enable them to proactively support independence and aging in place. This will allow reducing stress, lowering costs and unnecessary assistance. Continuous

monitoring of individual parameters will allow earlier diagnosis and prevention of health problems in the future as well of acute emergency events.

Recent advances in telehealth offer great opportunities for older people enabling them to live independently in their homes receiving care and remote health assistance from family and healthcare providers. Important issues as patients' acceptance and accessibility must be addressed since the end users, particularly elderly, may not be able on accepting the technology as a tool for healing [9].

One great advantage of the system is to provide health care for a large group of people, where previously they were limited by time and distance from the patient. Regarding the technical, economical and clinical aspects of home based telemedicine numerous studies demonstrated the effectiveness of this technology[10].

As aged population is increasing in developed countries it is expected that more care and monitoring will be needed. The costs of these services are becoming more affordable and portable devices become smaller and more user-friendly. The design of interconnected devices and sensors must be non-obtrusiveness and can be comfortably worn. Also they must be reliable and not affect the movement of users.

The future of this technology will pass by making data communication faster, safer and more economical and optimization of reliability. The factors that could affect reliability are network disruption, the main cause of failure in telemedicine systems; link failures in the data transmission, performance of the network. Those main causes of failure are in the wireless link or hardware and this will be optimized in the future [9].

3.3 Signals acquired

OneCare Sensing is versatile product that can use sensors from different brands. In this section the sensors are depicted as an example of how the product works. Also more parameters could be measured using different sensors but this is dependent of the client requirements that are constantly being evaluated.

3.3.1 Electrocardiogram

The electrical activity of the heart over time can be recorded by an electrocardiograph thus producing an electrocardiogram (ECG) [11].

Electrocardiography is a fundamental part of cardiovascular assessment. It is an essential tool for investigating cardiac arrhythmias and is also useful in diagnosing cardiac disorders such as myocardial infarction [12].

The contraction and relaxation of cardiac muscle results from the depolarization and repolarization of myocardial cells. These changes are recorded via electrodes placed on the limbs and chest wall and are transcribed on to a graph to produce the ECG [12].

The typical elements in an EGC waveform are presented in Figure 1. These are the isoelectric line, a horizontal line when there is no electrical activity; segments, the duration of the isoelectric line between waves; and intervals, the time between the same segments of adjacent waves. The P-wave results from the depolarization of the atria. The QRS complex corresponds to the ventricular depolarization. The T-wave represents ventricular repolarization and the U-wave is caused by after-potentials that are probably generated by mechanical-electric feedback [13].

The PQ segment corresponds to electrical impulses transmitted through the S-A node, the PQ interval expresses the time elapsed from atrial depolarization to the onset of ventricular depolarization. The ST-T interval coincides with the slow and rapid repolarization of ventricular muscle. The QT interval corresponds to the duration of the ventricular action potential and repolarization. Then TP interval is the period for which the atria and ventricles are in diastole. The RR interval represents one cardiac cycle and is used to calculate the heart rate [13]. These elements are used to diagnose heart diseases.

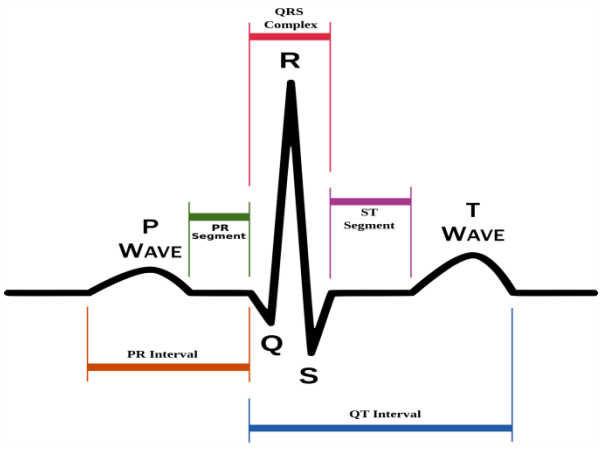

Figure 1 - Typical ECG wave [14]

The sensor used for this application is a low-noise ECG triodes that is specially design for local placement and allow signal acquisition. It is designed to maximize the sensor performance and providing high resolution signals for

fine detailed analysis. It works by detecting and amplifying small electrical changes on the skin that are caused during the heart muscle cycle during each heartbeat.

Figure 2 - EcgPLUX sensor [15]

This sensor is mostly used for heart rate and stress monitoring, biometric verification and life monitoring. It is also suitable for research applications [15].

3.3.2 Temperature

The normal temperature of a resting human is 37.0 degrees Celsius. Despite this, the value can vary due to an individual metabolism rate, age and time of the day. The higher the metabolism the higher will be the body temperature. Also it was proven that body temperatures are lower in the morning due to the rest the body received and higher at night after the day of muscular activity and food intake. Older people usually have lower body temperatures [16].

Body temperature also varies on the part of the body the measure is taken from. Oral temperatures are accurate and the most convenient. Axillary or between two folds of skin are external measurement that a take the longest and are very inaccurate. Rectal temperatures are the least time consuming and most accurate type of measurement but they are by far the least convenient [17].

This signal is important in order to detect as quickly as possible hyperthermia or hypothermia situations. Abnormal body temperature values can indicate disease, injury or pharmacologic activity. Clinicians can use this to assess infection, inflammation or antigenic responses. It can also be used as an indication of the efficacy of treatment [18].

Figure 3 - Fora IR21 Series - Ear and Forehead Thermometer [19].

The sensor used is a FORA IR21 Series – Ear and Forehead Thermometer depicted in figure 3. It offers quick and convenient monitoring detecting both forehead and ear temperature. This thermometer has many key features such as are fever alert, one second measurement time, 10 values of memory capacity, a long battery life and it can transmit data wireless with Bluetooth [19].

3.3.3 Blood glucose and pressure

Measure of blood glucose at home is usually done by people diagnosed with diabetes mellitius. Diabetes is likely to become one of the most prevalent and economically important diseases of the 21st century because of an increasing incidence of type 2 diabetes mellitus in the developed countries [20].

This disease is characterized by hyperglycemia that results from defects in the secretion and/or action of insulin. Generally, type 1 diabetes mellitus is accepted as autoimmune disease with triggering factors responsible for the development of autoimmunity. On the other hand, type 2 diabetes mellitus is associated with peripheral insulin resistance, problems in hepatic glucose production, abnormalities in glucose absorption and obesity. The main effects of the disease include long-term damage and failure of various organs [21]. It is a serious chronic disease that leads to a substantial reduction in life expectancy, decreased quality of life and increased costs of care [21].

In blood glucose self-monitoring technique a drop of blood is applied to a strip inserted in a meter. The drop of blood then produces an electrical current proportional to its glucose concentration. This technique has become an integral part of insulin treatment. It allows patients adjust their insulin dosage and helps

avoid hypoglycemia. This gives him a better control of his situation but there is not a consensus on how often patients should check their blood glucose [20].

Official hypertension guidelines acknowledged the value of blood pressure monitoring for the accurate diagnosis of hypertension. Self-monitoring has many advantages as it eliminates the white coat syndrome, a phenomenon in which patients exhibit elevated blood pressure in clinical setting but not in other settings due to anxiety, allows the increased number of readings and how the response to antihypertensive treatment is, reduces costs and improves patient compliance [22].

Systolic blood pressure has a strong tendency to increase with age, so the prevalence of hypertension also increase with age. Globally, high blood pressure accounts for more deaths than many common conditions and it is a major burden of disease.

Hypertension is related with genetic and environmental factors [23]. Environmental factors include salt intake, weight, alcohol consumption, stress and diet. Control of these factors is essential in preventing and in managing hypertension.

The increases of systolic and diastolic blood pressures are associated with different pathologies as stroke, which is one of the most devastating consequences of hypertension resulting in premature death or disability; dementia, elderly people are at risk of asymptomatic cerebral strokes that may lead to loss of intellectual or cognitive function and heart failure, where hypertension is the main cause.

Figure 4 - FORA D40d - Blood glucose plus blood pressure monitoring system [24]

The device used to monitor blood glucose and blood pressure is FORA D40d. The results can be stored in memory or transmitted to a computer or the internet for data management. It also allows Bluetooth connectivity – used by OneCare Sensing – and GPRS connectivity [25].

3.3.4 Pulse oximetry

Pulse oximetry is a noninvasive method for monitoring the saturation of oxygen in a patient. It is considered the ultimate safety monitor in anesthesia because it shows not only how well the patient is oxygenated but also that the blood is circulating [26].

The operating principle is that the absorption of light at two wavelengths differs according to the haemoglobin's degree of oxygenation. The measuring of light absorption occurs at 600-750 and 850-100 nanometers. The ratio between the two is then computed giving the measurements of arterial blood oxygen saturation [26].

There are various types of hypoxia but the hypoxic hypoxia, which occurs when arterial haemoglobin oxygen saturation is low, is the only form that can be detected by the pulse oximeter. There are three main causes of failure of oxygenation of the blood by the lungs, low partial pressure of inspired oxygen, pulmonary causes and cardiovascular causes. Related to these causes of failure it is possible to associate several pathologies such as chronic bronchitis, asthma, pneumothorax, sleep apnea, pneumonia, emphysema, cardiac failure, amongst many others. An alarm is triggered when the oxygen saturation is below 95%.

The most obvious advantages of this technology are that it is fast, accurate and non-invasive and reliable. Regarding disadvantages, the inefficacy in poor perfusion states, in anemia, color interference, skin pigmentation and motion artifacts needs to be considered.

Figure 5 - Nonin 4100 Bluetooth enabled digital pulse oximeter [27]

The device that accomplishes this is Nonin 4100 bluetooth enabled digital pulse oximeter that allows SpO2 , pulse rate and plethsmographic data to be transmitted through Bluetooth to the tablet used in OneCare Sensing. The maximum range of the device is around 9 meters (spherical radius) [28].

3.3.5 Respiratory parameters

Spirometry takes measurements of the quantity of air inhaled and exhaled by the lungs during a certain period of time to determinate the pulmonary capacity. It is the most valuable test for assessment of patient with chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases and other respiratory diseases, preoperative and occupational risk [29]. OneCare Sensing will assess the prevention and monitoring of COPD.

COPD covers at least three factors: chronic bronchitis, emphysema and progressive obstruction of the small airways. It is characterized by slowly progressing, mainly irreversible airways obstruction and a decreased expiratory flow rate. The decreased flow rate is caused by varying degrees of airways obstruction and emphysema [30].

Spirometry measurements for the diagnosis of COPD include: forced vital capacity (FVC), maximum volume of air that can be exhaled during a forced maneuver; forced expired volume in one second(FEV_1), the volume expired in the first second of maximal expiration after a maximal inspiration and the ratio between those two indicates airflow limitation and thus COPD [31].

Figure 6 - Vitalograph copd-6 [32]

One device that can be used for effective COPD screening is Vitalograph copd-6™ that identifies those at risk of COPD at the pre-symptomatic stage to allow early medical intervention and provide better clinical outcomes. It can screen identify those for which FEV_1 is normal without the risk of false COPD negatives [32].

3.3.6 Body mass

Body mass index (BMI) is defined as the individual' s body mass divided by the square of their height given in units of kg/m^2. It should be measured and record as any other vital sign as a practical way to identify individuals who are overweight or obese. Overweight is defined with a BMI between 25 and 29 kg/m^2 and obese with one greater than 30 kg/m^2. Genetic and environmental causes are in the heart of risks of this epidemic [33].

Table 3 – Weight classification adapted from [33]

Classification	BMI	Obesity Stage
Underweight	≤18.5	-
Normal	18.5 to 24.9	-
Overweight	25.0 to 29.9	-
Obesity	30.0 to 34.9	I
	35.0	II
Extreme obesity	≥40.0	III

Excess weight is associated with pathologies such as stroke, type 2 diabetes, endometrial, breast and colon cancer and also increases the risk of liver and

gallbladder disease, sleep apnea, osteoarthritis and gynecologic problems such as infertility [33].

Although BMI correlates with the amount of body fat it does not differentiate fat from muscle. It is important to identify more factors as diseases associated with obesity, such as high blood pressure, physical activity and waist circumference as a measure of abdominal adiposity [34].

Figure 7 - FORA W310b Weight Scale [35]

The weight scale used is FORA W310b that features high accuracy and many functions as Bluetooth data transmition, body weight and BMI measurements, conversion of weight units (Kg/st/lb) and it can store up to 135 results [35].

4 State of the art

The state of the art given is more focused in the market of remote patient monitoring products. It is essential to understand how the market is structured in order to know how to deploy the product that is being certified in the best possible manner. Therefore the following chapter presents a compilation and review of different studies that are considered relevant to the remote patient monitoring and treatment (RMT) market as the state of the art.

Firstly an introduction to some key concepts and background is given. Then a market overview is presented to show some facts and numbers considered relevant. After this the constitution of the main players, Horizon 2020 program, a sample of market products similar to OneCare Sensing and the difficulties and barriers in this market are showed.

4.1 Introduction

It is predicted that the patient monitoring market is going to growth significantly in the next years. As reported by several market studies the devices that measure patient' s vital signs across the patient' s house or hospital building are the fastest growing medical devices in terms of revenue earned. According to one of them, revenues have doubled in the last four years and it is expected to double in the next four. To demonstrate part of this statement, a growth of 23% between 2008 and 2010 was seen in the remote and wireless patient monitoring devices [36].

The European health systems differ a lot from country to country but despite this they have common objectives such as universality, access to good quality care, solidarity and equality they also share common challenges [37]. One that is relevant to refer is population ageing – with the increase of this segment in the population there will be more people with chronic diseases that require routine monitoring which consequently increases healthcare costs [38]. Also according to the Eurostat Labor Force Survey there is going to be a lack of qualified personal in the area of Health and Social work such as physicians and nurse graduates. This factor presents a lack of human resources that will also contribute to the difficulty in treating the increasing ageing population with chronic diseases.

In the EU the funding in healthcare rely in three different methods. The Beveridge model, focused in public taxation. The Bismark model, focused in

compulsory social insurance. And the third is based on voluntary private insurance that complements the social insurance. The increase of healthcare costs will overload these models and it is necessary to take measures in order to maintain a sustainable system [38].

The most relevant chronic diseases that are important to discuss are diabetes, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD) because they are targeted by RMT and have economical relevance [39]. The impact of cardiovascular diseases is estimated to be 192 billion euros a year in Europe [40].

Telemedicine and more specifically RMT devices aim to decrease the costs mentioned above, related with cutting hospital stays, deal with reduced staff and reduce human errors. According to the Strategic Intelligence Monitor on Personal Health Systems (SIMPHS) joint research center of European Union, RMT systems " help patients with chronic diseases monitor vital signs (blood pressure, heart rate, blood glucose, weight, oxygen contents, ECG) thus improving the quality of care, the quality of life of the patient and prediction of aggravations and exacerbations of their chronic condition." Also it is important to understand what IPHS is, " Integrated Personal Health/Care Services address the health and/or social care needs of individuals outside of care institutions and support the work of care providers in an integrated fashion: a) they can integrate assistance, remote monitoring of chronic diseases, wellness and fitness; b) they are produced as a result of integration of different institutional and information systems. They are personal and possibly personalized in the way they gather, process and communicate data (for feed-back/action) and in terms of technological components they can include all of the items illustrated a) trough c)" .

4.2 Market overview

According to an European study, currently the remote patient monitoring market is fragmented, small in size and it has a lot of social, economic and technical barriers [41]. Despite this there are a lot of different market reports that have an estimation of the real size and value of RMT.

According to Frost and Sullivan' s the remote patient in Europe in 2009 had the UK with a 25% market share and Germany with 21%. Other relevant markets are France, Italy and Benelux [41].

Also from a Transparency study, " Remote Patient Monitoring Devices Market – Global Industry Size, share, Analysis, Upcoming Technologies,

Current Trends And Forecasts 2012-2018" the remote patient monitoring market is expected to reach $556.9 million by 2016 with an annual growth of 10% in the selected period. The largest segment of the industry is cardiac monitoring which will constitute about 72% of the total market. The United States and Europe will be the main geographical areas where this growth is verified [42].

The remote patient monitoring can be segmented in two fields, telecare and telehealth. Telecare provides real time monitoring of emergencies and social care with support from communication technology. Telehealth provides remote monitoring of patient's vital signs through the use of medical devices [43].

Telehealth market is driven as stated before by ageing population and increasing of patients with chronic diseases. The need to manage patients in remote locations, the increase hospital expenses and decreasing number of physicians to assist patients are the driven forces to sustain this market.

RMT systems contribute in the following manner:

- Improve healthcare outcomes and simultaneously help control costs;
- Help reach healthcare to remote regions and solve the problem of short number of health care professionals;
- Improve job creation and entrepreneurial activities and innovation such as ISA-Intellicare.

4.3 Players

The players active in the RMT market segment are presented in annex 1. This company list was adapted from annex 3 of the " Strategic Intelligence Monitor on Personal Health Systems, Phase 2: Market Developments – Remote Patient Monitoring and Treatment, Telecare, Fitness/Wellness and mHealth" presented by the Joint Research Center of the European Commission from 2013. The adaptation was made by analyzing the products and services of each company and selecting the ones that are included in the RMT definition. It was discovered that 9 companies where bankrupt and 24 where not active in the RMT market.

The companies involved in the annex fulfill four main criteria of the study mentioned above:

- They played a relevant role in the RMT market;
- They had an European focus;
- They covered as many products and services as possible;

- They covered all parts of the PHS value chain.

Figure 8 shows the geographic distribution of the 81 RMT companies considered in annex 1. There are about 48 companies in Europe, 25 in the USA and the 8 remaining are reasonably divided by other countries.

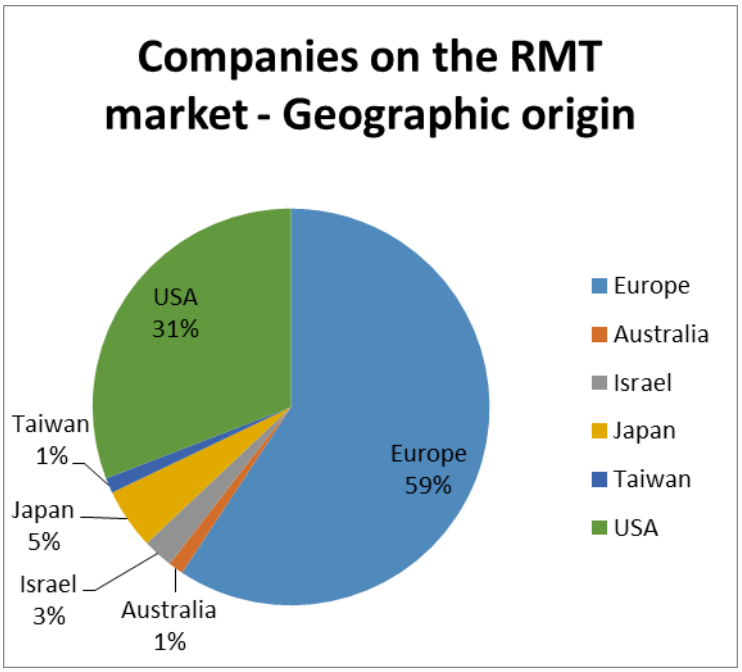

Figure 8 - Companies on the RMT market - Geographic origin

The market players that provide hardware solution for RMT can be divided in four main categories [43]:

- Medical engineering companies that demand higher quality products and invest significantly on staff qualifications especially R&D staff.
- Companies that modify existing products to enable them to be used by laymen. Usually this is done to extend their market scope.
- Pharmaceutical companies enter as new players since they can complement their product (drugs) with RMT adding more value to their service.
- Original Equipment Manufacturers (OEM), companies that manufacture products for other companies to be repackaged and resold with other name and logo.

Frost & Sullivan rated Germany and the UK as the European markets with the best short term opportunities regarding revenues. France and Italy also show good prospects and the others small markets will tend to grow. But in the long run it will be difficult to predict the RMT market in countries that rely in government subsidies since cuts on telehealth and telecare can be made.

4.4 Horizon 2020

In this section the next EU funded programs will be presented in order to show new investment opportunities and the economic relevance regarding the market being depicted.

The biggest European Union Research and Innovation program is Horizon 2020. It has around 80 billion euros on funding available from 2014 to 2020 not counting with the private investment that the programs will attract. It aims to secure Europe' s global competiveness and at the same time drive economic growth and create jobs [44].

Horizon 2020 is based on the societal challenges identified and shared by European citizens. This will put together a lot of resources and knowledge from different fields from a more technical approach to social sciences. The challenges according to the EU are [45]:

- Health, demographic change and wellbeing;
- Food security, sustainable agriculture and forestry, marine and maritime and inland water research, and the Bioeconomy;
- Secure, clean and efficient energy;
- Smart, green and integrated transport;
- Climate action, environment, resource efficiency and raw materials;
- Europe in a changing world - inclusive, innovative and reflective societies;
- Secure societies - protecting freedom and security of Europe and its citizens.

The challenge that is relevant to identify here is Health, Demographic Change and Wellbeing. It includes keeping older people active and independent by developing safer and effective solutions. During 2014 and 2015 the EU will invest around 1200 million euros only in this section of the program.

In order to be more specific the research & innovation team duties related to this call will be improving the understanding of healthy ageing and disease; improve the ability to monitor health, prevent, detect, treat and manage disease; support older people to remain active and independent and test and demonstrate models to health and care delivery [44].

The full work program for the next two years can be found in "Horizon 2020 Work Programme 2014-2015: 8. Health, demographic change and wellbeing" . In

the next table one can find a selection of calls, their proposition value and type of action that incorporate ICT and the program mentioned above.

Table 4 - List of calls in Horizon 2020

Calls		Proposition value (M€)	Type of action
PHC 19 - 2014	Advancing active and healthy ageing with ICT: Service robotics within assisted living environments	3 to 4	Reserach and innovation
PHC 20 - 2014	Advancing active and healthy ageing with ICT: ICT solutions for independent living with cognitive impairment	2 to 3	Innovation
PHC 21 - 2015	Advancing active and healthy ageing with ICT: Early risk detection and intervention	3 to 4	Reserach and innovation
PHC 25 - 2015	Advanced ICT systems and services for Integrated Care	3 to 5	Reserach and innovation
PHC 26 - 2014	Self-management of health and disease: citizen engagement and mHealth	3 to 5	Reserach and innovation
PHC 27 - 2015	Self-management of health and disease and patient empowerment supported by ICT	3 to 5	Pre-commercial procurement co-fund actions
PHC 28 - 2015	Self-management of health and disease and decision support systems based on predictive computer modelling used by the patient him or herself	3 to 5	Reserach and innovation
PHC 29 - 2015	Public procurement of innovative eHealth services	1 to 5	Public procurement of innovative solutions co-fund actions
PHC 30 - 2015	Digital representation of health data to improve disease diagnosis and treatment	3 to 5	Reserach and innovation
PHC 34 - 2014	eHealth interoperability	1	Coordination and support

Calls		Proposition value (M€)	Type of action
			actions
HCO 1 - 2014	Support for the European Innovation Partnership on Active and Healthy Ageing	1 to 2	Coordination and support actions
HCO 2 - 2014	Joint Programming: Coordination Action for the Joint Programming Initiative (JPI) "More Years, Better Lives - the Challenges and Opportunities of Demographic Change"	1 to 2	Coordination and support actions

4.5 Marketed products

This section will present some products currently being marketed that share one or more functions with OneCare Sensing. This is not supposed to be an extensive list nevertheless it can provide some useful information regarding the competition that exists in the RMT market today.

Alive Heart and Activity Monitor – This is a wireless health monitoring system for consumer health that can screen, diagnose and manage chronic diseases. The applications for the product include management of atrial fibrillation, heart failure, cardiac rehabilitation and fitness monitoring. The data gathered is transmitted wireless by Bluetooth to a mobile phone, computer or central monitoring center. Then it is available for consultation via internet [46].

Figure 9 - Alive Heart and Activity Monitor [46]

Aipermon Telemonitoring – A complete telemonitoring solution that is presented in the figure below. The AiperMonitor PC Software allows the access of the activity, weight, blood pressure, glucose, insulin and state of the health data [47]. The system is built with different modules that function togheter in order to automatically transfer the data to and hospital, medical call center or physicians.

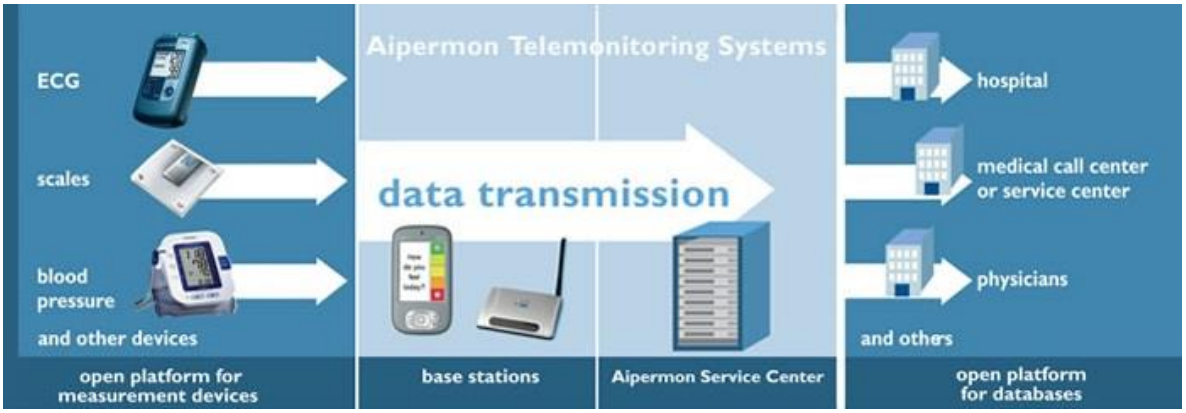

Figure 10 - Aipermon Telemonitoring [47]

Beurer's One 4 ALL – Beurer sensor's allows the data gathered to be transferred to a PC and smarthphones. The PC software enables to analyze the body values more closely and it has many functions that allow conveniently exporting or sending data to a doctor. The HealthManager APP as the same functions of the pc software [48].

Figure 11 - Beurer' s One 4 ALL [48]

BodyTel System – Is a telehealth product that supports and diagnoses patients with home chronic illnesses advised by healthcare providers. It uses sensors with an integrated Bluetooth module to measure blood glucose levels, arterial pressure and weight. Then data is sent to a patient's cell phone or tablet and posteriorly to a database to be consulted by others. The system also as an alarm option that is triggered when physiological parameters fall under a certain threshold [49].

Figure 12 - BodyTel System [49]

Bosch Telehealth system – Each day there is a new session where the patient can gather his vital signs, review sympthoms, take surveys, have an educational coaching and reinforcement of positive behavior. The vital signs are gathered with a wireless sphygmomanometer and a pulse oxymeter. The system can access depression, CHF and COPD. The system can send data to a healthcare provider for further assessment [50].

Figure 13 - Bosch Telehealth system [50]

Dyna-Vision Telemonitoring System – Designed for remote monitoring of ECG, SpO2, temperature, respiration rate and blood pressure. It transmits the values in real time to a server and various alarms can be defined for each parameter. Data is stored in the PC and in the cloud to generated PDF reports [51].

Figure 14 - Dyna-Vision Telemonitoring System [51]

BodyGuardian Remote Monitoring System – Where the patients wear a control unit that transmits data by wireless to a smartphone device. Then data is available in a Preventice CarePlataform, a cloud-based plataform that collects real-time data and delivers this information to healthcare professsionals. It monitors patient ECG, respiration rate, activity level and body position [52].

Figure 15 - BodyGuardian Remote Monitoring System [52]

4.6 Difficulties and barriers

The main barriers reported by market players mentioned in the JRC Scientific and Policy Reports, " Market Developments – Remote Patient Monitoring and Treatment, Telecare, Fitness/Wellness and mHealth" are the following:

- Lack of reimbursement – A major obstacle on the market because of the costs associated with the technology.
- Buyers' fragmentation – The diversity of healthcare financial structure in Europe results in decentralized and different ways companies sell their products and services.
- Difficult to be accepted by health care organizations – There is resistance from health care providers to accept RMT products/services.
- Constrains to market scale – The buyers' fragmentation mentioned before is reflected in a difficult escalation of the market.

The barriers identified by individuals in the health care systems or by neutral third party experts are:

- Unfavorable structure of incentives – The overall financial incentives structure in EU countries run against RMT. There are two models, fee for service or capitation. Fee for service pays the fee for services the hospital receives and since RMT aims to keep patients out of the hospital this is not a good model. In the capitation model usually general practitioners are paid for managing a set of patients and they see RMT service as and extra an unpaid load.

- Where RMT belongs – There is much talk about the importance of this form of care but politicians and policy makers need to implement measures to adopt RMT.
- Lack of evidence, awareness, education – There is a lot of evidence supporting RMT but the results are not conclusive. More work in raising awareness and education needs to be done not only for physicians but also patients that will use this technology.
- Strategic leadership for structural change – There is a need for strategic leadership and decision for making the delivery of RMT more efficient and effective.

To sum up the main restrains in the market are the lack of common European standards, high costs of deployment of the technology, lack on information on funding and reimbursement and the resistance to IT from healthcare professionals.

5 Medical device certification in EEA and other European countries

In the following chapter it is introduced the regulatory framework for the product OneCare Sensing and the most efficient way to obtain CE marking in order to market this product in Europe. This is the most detailed chapter in the thesis since all the practical work made in the internship falls under this scope.

5.1 CE marking

The CE mark in a product is a manufacturer' s claim that it meets the essential requirements of the applicable directive and it is a legal mandatory requirement to place a medical device in the European market [53]. The countries that recognize this marking are in the European Economic Area, Switzerland, Macedonia and Turkey. The EEA includes the 28 member states of the EU plus the european free trade association; Switzerland regonizes CE marking as national law; Macedonia and Turkey are candidates to become European Union members.

CE marking is not an indicator that a product was made in Europe, it only states that the product was assessed before being placed in the market according to the legal applicable requirements enabling it to be sold here [53].

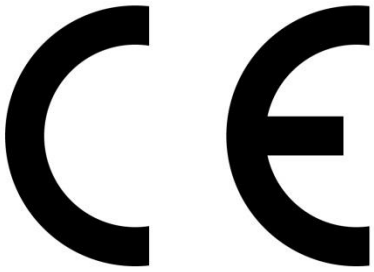

Figure 16 - CE marking logo [54]

5.1.1 Key players

The key players involved in the CE marking process are the following:

- Manufacturers, responsible for manufacturing activities related to a device that is being placed on the market under the manufacturers' name [55].

- Competent authorities, national authority that assures the medical devices sold in that country satisfy the essential requirements established in the directive – in Portugal is INFARMED, *Autoridade Nacional do Medicamento e dos Produtos da Saúde I.P.*

- Notified Bodies, third party organizations that carry out conformity assessments in European harmonized standards or European Technical Assessment. Their tasks include product certification, factory production control certification and determination of the product-type on the basis of type testing [56].

- Authorized representative, is a natural or legal person established in the EU designated by a non-European manufacturer to act on its behalf regarding some tasks designated by the directives [57].

- Distributors, natural or legal person who makes available medical devices to the end user [58].

- Laboratories, they perform analysis and evaluation of trials following certain standards to guarantee the safety of the device.

5.2 Process overview

In figure 17 are presented the necessary steps in order to obtain CE marking for OneCare Sensing. These steps could apply to other products but here they are specific to the product being analyzed. They will be discussed more specifically in the next section.

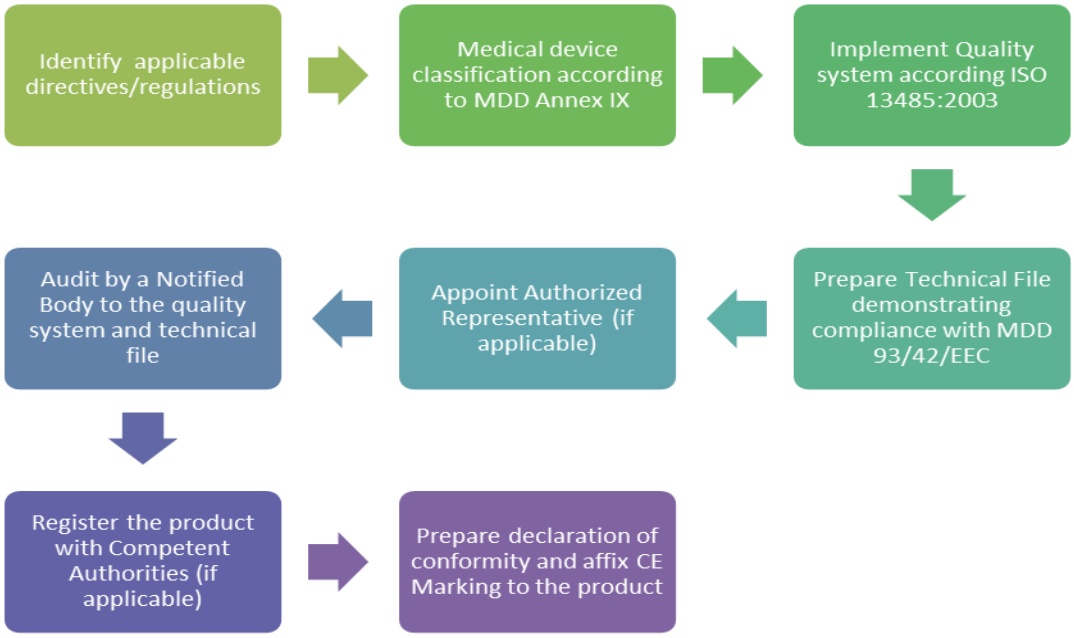

Figure 17 - Steps to obtain CE marking

5.3 Identify applicable directives

Rules relating to the safety and performance of medical devices in the EU consist of 3 Directives:

- Directive 90/385/EEC regarding active implantable medical devices;
- Directive 93/42/EEC regarding medical devices reviewed and amended by the 2007/47/EC;
- Directive 98/79/EEC regarding in vitro diagnostic medical devices.

They aim ensuring a high level of protection of human health and safety and the good functioning of the health market. Each one of these directives is transposed to national law by their members. In Portugal the national law for the directive 93/42/EEC is *Decreto-Lei n.º 273/95, de 23 de Outubro* . In a very superficial analysis it was verified that this law is a simple translation of the directive.

After being aware of these directives it could be simple to conclude that directive 93/42/EEC regarding medical devices is the one applicable to our product. But in order to be sure it is essential to qualify if OneCare Sensing is, in fact, a medical device.

In order to have a proper qualification of the product it is important to understand what a medical device is. To do this one must refer to Article 1.2(a) of Directive 93/42/EEC [59] known as the medical devices directive. By their definition,

" (a) ►M5 ' medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: ◄

—diagnosis, prevention, monitoring, treatment or alleviation of disease,

—diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

—investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;"

After being aware of this definition it was read the MEDDEV 2.1/6 January 2012 - Qualification and Classification of stand alone software [60] in order to qualify the product correctly.

Regarding chapter 1 " Definitions and abbreviations" in the above guideline, the product OneCare Sensing is a standalone software once the tablet where the software is implemented is not a medical device.

By analyzing " Figure 1: A decision diagram to assist qualification of software as medical device" of MEDDEV 2.1/6 [60] the decision steps made were,

Question.1. " Is the software a computer program? (cf. ISO/IEC 2382-1)"

Answer.1. The software used is indeed a computer program.

Q.2. " Is the software incorporated in a medical device?"

A.2. No. The tablet where the software is implemented is not a medical device.

Q.3." Is the software performing an action different from storage, archival, lossless compression, communication or simple search?"

A.3. Yes. The software is providing alarms based on the data acquired.

Q.4. " Is the action for the benefit of individual patients?"

A.4. Yes. View intended use.

Q.5. Is the action for the purposes defined in art 1.2a of MDD?"

A.5. Yes. View definition of medical device.

It is concluded that OneCare Sensing with alarms is covered by medical device directives.

Also, using the same guide, in annex 3.1. about the Clinical Information Systems – CIS / Patient Data Management Systems – PDMS [60],

" Modules that are intended to provide additional information that contributes to diagnosis, therapy and follow-up (e.g. generate alarms) are qualified as medical devices."

With this information it is justified that OneCare Sensing with alarms is a medical device.

5.4 Medical device classification

Medical device classification is divided in four risk classes showed in figure 18. Determine product classification is one of the most important tasks of the work because it dictates which are the next steps to follow in order to obtain CE marking. These steps include if it is needed the intervention of a notified body and the way compliance is achieved within the directive.

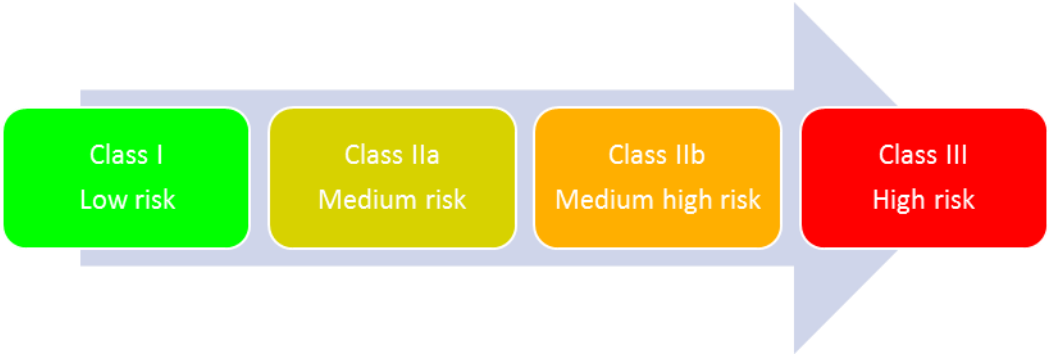

Figure 18 - Medical device class's according to risk

The classification criterion is based on a set of 18 rules presented in Annex IX of the MDD. In order to establish a proper classification of the product it is important to understand its intended use, characteristics and the technology behind it.

In accordance with section 1.4 of Annex IX of the European Directive 93/42/EEC [59], stand-alone software is considered to be an active medical device. OneCare Sensing with alarms is, therefore, due to its characteristics an active, non-invasive, medical device. The rules applied to active medical devices in the previous annex are rules 9, 10, 11 and 12. To be more specific only rule 10 is pertinent to OneCare Sensing:

Rule 10 - " Active devices intended for diagnosis are in Class IIa: (…)

- if they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which they are class IIb. (…)"

Since this is a very vast definition, a guide on the applicability of the rule was followed. These guidelines are the Guidance MEDDEVs that aim to promote a common approach by manufacturers to the medical device directives.

By the intended use of the device and MEDDEV 2.4/1 Rev.9 June 2010 – Classification of medical devices, Chapter 4.2. General explanation of rules/pratical issues/examples, rule 10, note 1 [61],

" Note 1: Vital physiological processes and parameters include, for example respiration, heart rate, cerebral functions, blood gases, blood pressure and body temperature. Medical devices intended to be used for continuous surveillance of vital physiological processes in anesthesia, intensive care or emergency care are in Class IIb, whilst medical devices intended to be used to obtain readings of vital physiological signals in routine check ups and in self-monitoring are in Class IIa. A thermal imaging device intended to monitor blood flow is not considered to be a temperature measuring device."

It is concluded that OneCare Sensing with alarms is classified as an active medical device of Risk Class IIa, based on Rule 10 (Active devices intended for direct diagnosis) of Annex IX of the European Directive 93/42/EEC.

The table below tailors the rules of Annex IX of European Directive 93/42/EEC with respect to the risk classification of OneCare Sensing.

Table 5 - Rules of Annex IX of MDD applied to OneCare Sensing

Nr.	Rule	Applicability
I. – 1.6	Active device for diagnosis	Yes
II. – 3.2 Rule 10	Active devices intended for diagnosis are in Class IIa:	Yes
	If they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum.	No
	If they are intended to image in vivo distribution of radiopharmaceitucals.	No
	If they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac	Yes, although the software is not used for direct diagnosis

	performance, respiration, activity of CNS in which case they are in Class IIb.	
	Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.	No

5.5 Conformity assessment route

After the classification of the product the manufacturer must choose the conformity assessment procedure that is laid out in article 11 of the MDD. For a class IIa device there are four possible ways to demonstrate the conformity with the directive:

- Annex VII + Annex IV (EC verification);
- Annex VII + Annex V (production quality assurance);
- Annex VII + Annex VI (product quality assurance);
- Annex II (full quality assurance) with point 4 of the annex not applicable.

The route chosen was the Full quality assurance (Annex II) with the exemption of point 4. The next section will show how its implementation can be achieved inside the company.

5.5.1 Compliance with annex II of the MDD

The compliance route with annex II of the directive 93/42/EEC was chosen. This ensures the application of a quality system approved for the design, manufacture and final inspections of the product and must be audited by a notified body after its implementation. This annex is divided in the three next sections.

Quality system

This section refers that the manufacturer must apply to the notified body to assess the quality system. This application must ensure that the product complies with the directive since design to production. These elements such as documentation, data, records, etc are presented in this section. Also refers the

importance of having a post-production phase to implement necessary corrective actions if the product malfunctions or has performance issues.

Surveillance

The manufacturer must allow notified body inspections and supply all the necessary information to check if the obligations imposed are being fulfilled.

Administrative provisions

The documentation such as the declaration of conformity, quality systems manuals and technical file must be available for the national authorities for at least five since the product manufacturer date.

5.6 Implement quality system according to ISO 13485:2003

In order to implement the quality system mentioned above the manufacturer could use ISO 13485:2003. This quality management system, specific for medical devices, is described in one of the following sections. It is important for a manufacturer to use this standard because of regulatory purposes and to provide better quality for their products and services.

5.7 Technical file

The requirements for the technical file are spread in the annexes of the directive so it was used the recommendation "2.5.1 Conformity assessment procedures; General rules from NB-MED" [62] in which a recommended structure for the documentation is given.

This structure was adapted since some details related with the technical point of view were not applicable to OneCare Sensing. The file compiled can be viewed in annex 2 and the index is shown below:

1 Introduction
- 1.1 Objectives
- 1.2 Manufacturer
- 1.3 OneCare Sensing Research & Development
  - 1.3.1 OneCare Sensing Related Scientific Papers
- 1.4 Regulatory frame of reference
- 1.5 References
  - 1.5.1 Applicable Documents
  - 1.5.2 Reference Documents

2 Product Description

2.1 General description of the device

2.2 Intended Use

2.3 Description of the accessories which are intended by the manufacturer to be used in combination with the device

2.4 Classification of the device

3 Technical Requirements

3.1 Identification of technical requirements

3.2 Essential requirements checklist

3.3 Standards applied

4 Design

4.1 Risk analysis results

4.2 Specifications of the checks, tests and trials that are intended to be carried out as part of routine production

4.3 Performances and compatibilities intended by the manufacturer

4.4 Labelling, including any instructions for use

4.5 Results of Bench Testing

4.6 Clinical evaluation

4.7 Documentation and reporting of Design Changes

5 Administrative details

5.1 Declaration of conformity

5.2 Application for Conformity Assessment

5.3 Declaration that no other Notified Body is used in Conformity Assessment

5.4 Notified Body Decisions and Reports

5.5 Manufacturer' s undertaking on procedure to review post-production experience

6 Annexes

Because of the relevance of some of these points such as section 3 – Technical Requirements, section 4.1. Risk analysis and 4.6 Clinical evaluation they will be addressed individually through this document.

5.8 Appoint authorized representative

If a company does not have presence in the EU, which is not the case of ISA, the directive for medical devices mandates that a European Authorized Representative (EC Rep) located in Europe must be appointed. Their tasks are

only of administrative nature and it is the manufacturer responsibility to assure compliance according production and technical documentation [63]. The EC Rep should be consider as a bridge that establishes communication between the company that wants to market the product and the European regulatory authorities.

5.9 Audit by a notified body

The implemented quality system in the company and the technical file must be audited by a Notified Body in order to verify that they comply with the directive. After the successful audit the Notified Body will issue a CE certificate [64].

5.10 Register product with competent authorities

Some countries such as the UK and Italy require registration of the medical product with the Competent authorities. They should be contacted before the marketing of the product in order to see if this step is necessary. A list with the contacts of the various authorities is provided in [65]. When the device does not function properly the competent authority is responsible to remove it from the market.

5.11 EC declaration of conformity

A CE declaration of conformity must be prepared by the manufacturer to sell medical devices in Europe. A template for this declaration is presented in annex 3. The elements included are [66]:

- Name of the device;
- Manufacturer's name and address;
- Name of company quality management representative;
- Name and identification number of the notified body;
- Name, address and phone number of European Autorized Representative (if applicable);
- CE Marking certificate number;
- Conformity assessment route to compliance, classification of the product and rule(s) number(s);
- Standards applicable;

- Name and signature of a senior management representative and date signed.

After this the manufacturer is able to affix CE marking to the product. It is important to mention that usually the CE certificates issued by the notified bodies have a validity of three years and ISO 13485:2003 certification must be renewed annually. There is also an annual audit from the notified body and if the company fails to pass CE marking privileges are revoked.

5.12 Overview of contact with notified bodies

In the official website of the European Commission and part of Europa – the official EU website is located the list of notified bodies that apply the legislation 93/42/EEC Medical devices [67]. By October of 2013 it contained 76 entities. This list provides useful information as the body type, name and country.

It was made a file presented in annex 6 with the information from above plus the contacts used in the process of medical device certification. After this five companies where excluded from our list because the contact with them could not be made.

In the beginning of the internship the notified bodies where contacted individually by email in order to respond to some questions that showed up in the course of the work – information about the device was also provided. These where,

1. We have two types of solutions. One is OneCare Sensing with and without alarms. Are they both medical devices?
2. Which guidelines do you recommend in order to do the classification of the device?
3. Is the international standard IEC 62304 the only one applicable for this situation?
4. Which is the duration from submission of required registration documents until approval for CE marking is officially granted by your Notified Body? How much will this process cost?

The response rate was about 40% and the content varied. From these responses it was found that 4 companies were not able to work in the scope of medical software certification. Despite classification of the device was not questioned some notified bodies provided their opinion on the subject.

Regarding question 1,

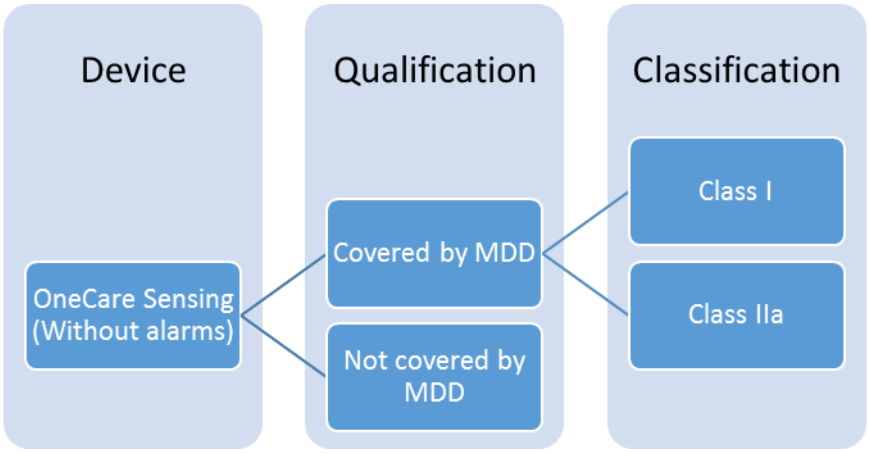

Figure 19 – Notified bodies opinion on qualification and classification of OneCare Sensing without alarms

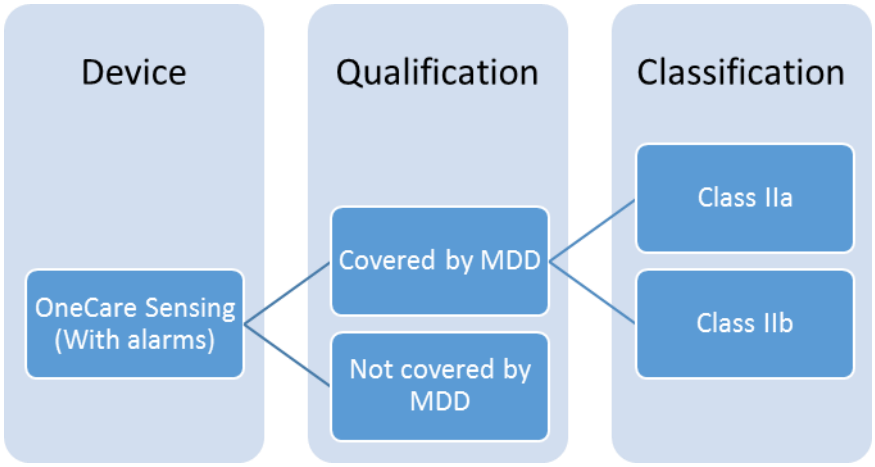

Figure 20 – Notified bodies opinion on qualification and classification of OneCare Sensing with alarms

Regarding question 2, the guidelines recommended where,

- MEDDEV 2.4/1 - Classification of medical devices;
- MEDDEV 2.1/6 - Qualification and Classification of standalone software;
- Manual on borderline and classification in the community regulatory framework for medical devices;
- Recommendation NB-MED/2.2/Rec4 – Software and medical devices;

Regarding question 3, the most relevant international standard applicable to this device where,

- IEC 62304 – medical device software –software life cycle processes;
- ISO 13485:2012 – Medical Devices – Quality Management Systems;
- ISO 14971:2012 – Risk Management system for medical devices.

Regarding question 4, the average cost and duration from submission to approval for CE marking is presented,

Table 6 - Review of notified bodies CE marking costs

	Cost (€)	Duration (weeks)
Max	5000	24
Min	3000	8

It is important to refer that it was necessary to provide more information about the process in order to have a more specific idea on the duration and costs but it was not available at the time. Also the costs presented in the table do not include ISO 13485:2003 certification.

5.13 Essential requirements

An important step in order to obtain CE marking is the compliance with the essential requirements of the directive. These requirements are laid out in Annex I of the medical devices directive and they describe safety objectives of the device [59].

The structure of the requirements is the following:

- General requirements
- Requirements regarding design and construction
    - Chemical, physical and biological properties;
    - Infection and microbial contamination;
    - Construction and environmental properties;
    - Devices with a measuring function;
    - Protection against radiation;
    - Requirements for medical devices connected to or equipped with an energy source;
    - Information supplied by the manufacturer.

Some of these requirements are not applicable to medical software so it is the manufacturer responsibility to assess this. All the requirements are mandatory unless they are not applicable.

In order to assess compliance the company should use a checklist that contains the essential requirements that identified those applicable and not applicable. For those applicable it should also contain the standards that could be use and the technical documentation necessary to ensure compliance [62]. The essential requirements checklist for the product OneCare Sensing can be found in annex 2.

5.14 Clinical evaluation

Clinical evaluation is an important step to obtain CE marking and it is part of the mandatory essential requirements contemplated in article 6a of annex I of the MDD. It also refers the annex X that is specific for clinical evaluation. Clinical evaluation is essential in order to demonstrate that safety and performance requirements of the device are achieved [68].

Since the law is not very specific, in order to comply with this part of the directive a guide of the Co-ordination of Notified Bodies Medical devices was used [68].

Clinical evaluation is defined as, "the process by which clinical data from all selected sources (literature, results of clinical investigations and other) is assessed to establish conformity of the device with the pertinent essential requirements of the Directive, and to demonstrate that the device performs as intended by the manufacturer. The outcome of this process is a report which includes a conclusion on the acceptability of risks and side effects when weighed against the intended benefits of the device."

There are three options that can be chosen in order to do the clinical evaluation, these are:

- Literature route, based on the relevant scientific literature.
- Clinical investigation route, based on the results of clinical investigations made.
- Combination on the previous two statements.

The manufaturer is responsible to decide which one of these routes is most pertinent in order to demonstrate conformity with the directive. It was decided that for the product OneCare Sensing the literature route was the most appropriate to follow.

Literature route

This route consists in a review of the relevant scientific literature. It is recommended that the compilation should be related with the hazards identified in the risk analysis, include favourable and unfavourable data, other type of scientific data such as bench testing and assessment of compliance with technical standards and for simple or well-established devices it should include experts' opinions regarding the device. Since this type of technology is not weel establish the last item is excluded.

A written report containning the clinical evaluation is required. The one elaborated for the product OneCare Sensing is presented in annex 7.

6 Normative framework

The medical devices directives specify their essential requirements in very general terms, standards are guides for the manufacturer to help achieve compliance. They provide a technical and legal interpretation of the requirements [69].

The essential requirements of the directive where analyzed and a list of the standards applicable to OneCare Sensing was compiled. These are:

- EN ISO 9001:2008 – Quality management systems – Requirements;
- EN ISO 13485:2003 – Medical devices – Quality management systems – Requirements for regulatory purposes;
- EN ISO 14971:2007 – Medical devices – Application of risk management to medical devices
- EN IEC 62304:2006 – Medical device software – Software life cycle processes

6.1 EN ISO 9001:2008

ISA-Intellicare has currently implemented a quality management system based on ISO 9001:2008. This standard is used when an organization needs to provide products that meet customer and regulatory requirements; and to enhance customer satisfaction through the application of the system. The requirements of the standard are generic and intended to be applicable to all organizations regardless of their size, type or product/services provided [70].

Figure 21 - NP EN ISO 9001:2008 Certification that could be obtained by ISA-Intellicare [71]

6.2 EN ISO 13485:2003

This European standard provides means for which a manufacturer can demonstrate conformity with the requirements of Directive 93/42/EEC on medical devices. It specifies requirements for a quality management system for the design, development, production, installation and servicing of medical devices or related services [72].

The objective of the standard is to facilitate harmonized medical device regulatory requirements for quality management systems. ISO 13485 is considered as an extension of ISO 9001 but it has some particular requirements for medical devices and exclusions of requirements that are not considered appropriate [72].

This quality management system was partly implemented in ISA-Intellicare and could be certified when the organization finds it more appropriate. It is recommended to perform an internal audit before the submission to the certification to avoid non conformities.

Figure 22 - ISO 13485:2003 Certification that could be obtained by ISA-Intellicare [73]

6.3 EN ISO 14971:2007

This International standard provides manufacturers with a framework to manage the risks associated with the use of medical devices. Primarily risks related with patients but also operators, other people, equipment and the environment.

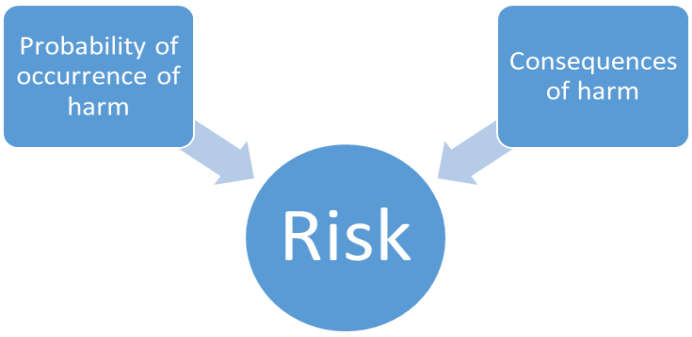

Figure 23 - Definition of risk

This standard specifies a process for the manufacturer to identify hazards, estimate and evaluate risks associated with these hazards, control the risks and monitor the effectiveness of that control related to a medical product during their life-cycle [74]. The risk analysis and the procedure written based in this standard are presented in annex 4 and 5, respectively.

6.4 EN IEC 62304:2006

This standard is applied to the development and maintenance of medical device software. It defines the life cycle requirements for the software and sets processes, activities and tasks providing a common framework for medical device software life cycle processes [75].

Under this standard it is assumed that the software is developed and maintained within a quality management system and a risk management system.

The norm focus is in the processes for development, maintenance, risk management, configuration management and problem solution of medical software. These are depicted in the figure below:

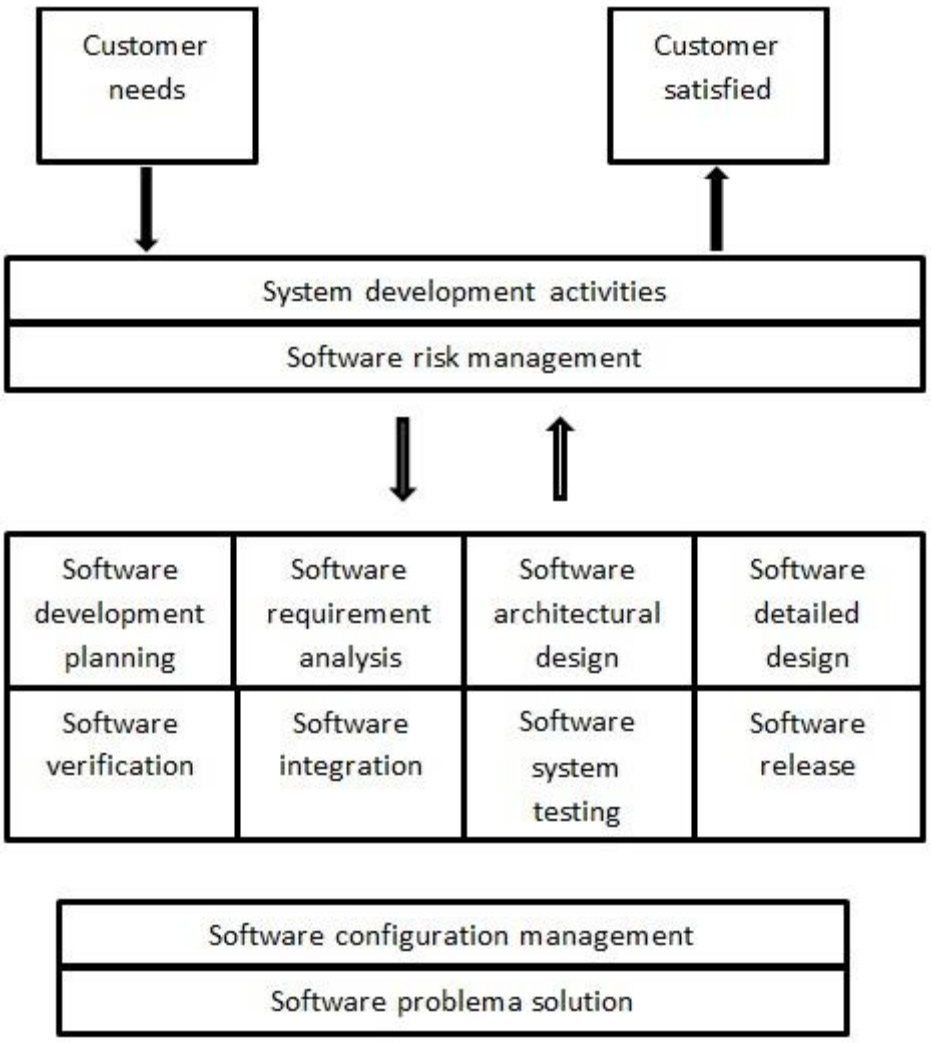

Figure 24 - Overview of software development processes and activities [76]

6.5 ISO 9001:2008 VS ISO 13485:2003

6.5.1 General

The purpose of this chapter is to present the fundamental differences between the quality management systems based on ISO 9001:2008 and ISO 13485:2003. This is relevant because ISA is currently ISO 9001:2008 certified but in a near future also wants to be ISO 13485:2003 certified in order to demonstrate the ability to provide medical devices and related services that meet customer and regulatory requirements.

The previous two standards where analyzed and compared in order to identify the gaps between the two of them. After this the necessary measures to

comply with ISO 13485:2003 where identified and some implemented (view annex 8).

The next figure presents the model for a quality management system following ISO 9001:2008. This model follows a process approach in which the main processes are:

- Quality management system
- Management responsibility
- Resource Management
- Product realization
- Measurement, analysis, improvement

The main input for this system is customer requirements and the output is customer satisfaction. These processes are common to both standards but in each one there are differences that will be addressed during this chapter.

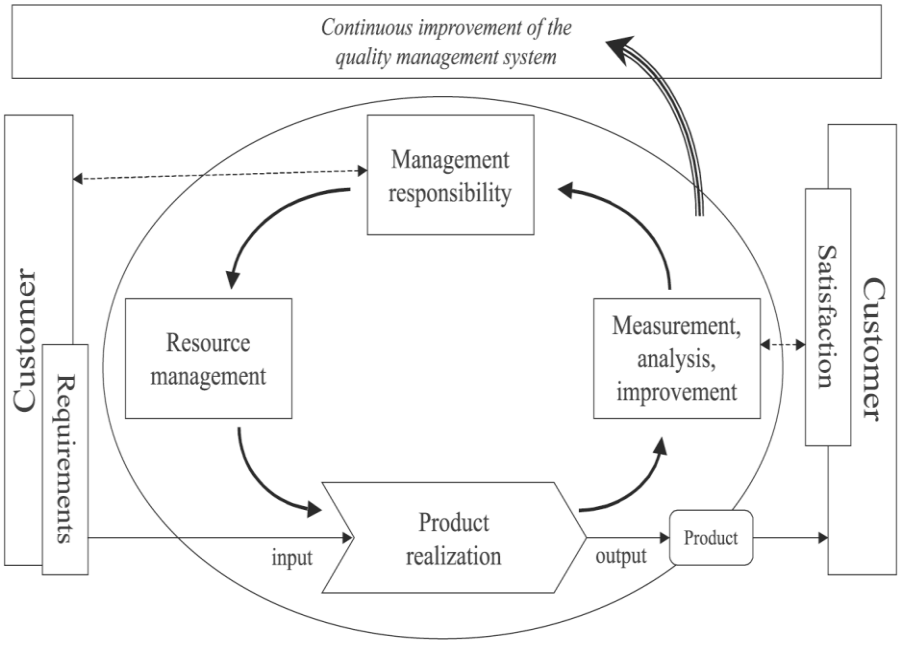

Figure 25 - ISO 9001:2008 process approach [77]

Despite ISO 13485:2003 is a standalone standard it is based on ISO 9001:2008. This means that a lot of requirements of ISO 9001:2008 are also presented in the standard of quality management systems for medical devices.

The main objective of ISO 13485:2003 is to facilitate harmonized medical device regulatory requirements for quality management systems [72]. Because of this, it includes new requirements and excludes others presented in ISO 9001:2008 that are not appropriate for regulatory requirements.

It should be noted that the specific standard requirements and company documentation are not presented in this thesis. This chapter represents only an

opinion of the author regarding the standards and what it is observed in the industry taking ISA as a general example.

6.5.2 Quality management system

The requirements for the quality management system are presented in the next figure. The general requirements are fundamentally the same in both standards and their implementation is usually verified during an audit.

The fundamental differences are in the documentation requirements. To comply with 13485:2003, documentation specified by national and regional regulations regarding the medical product/service should be included. Documentation that defines the complete manufacturing process, installation and servicing should also be maintained.

The Quality Manual must include all the exclusions and non-applicable requirements with a detailed justification. A procedure with the structure of the documentation used in the quality management system must also be provided.

Regarding the control of documents in ISO 13485:2003 it is necessary not only to approve documents prior to issue but also to review them when necessary. This can be demonstrated in an operational procedure made specifically for the control of records where it can also be defined the period for which a copy of the documents is obsolete.

The control of records adds a requirement for which the period of time that these records must be maintained.

General requirements	
Documentation requirements	General
	Quality manual
	Control of documents
	Control of records

Figure 26 - Quality management system requirements

6.5.3 Management responsibility

The requirements for the management responsibility are presented figure 27. Regarding management commitment, customer focus and quality policy the requirements are essentially the same with the difference that in ISO 13485:2003 the focus is in maintaining the effectiveness of the quality system and not

improving it as it is presented in ISO 9001:2008. These are usually checked during an audit.

The planning regarding management responsibility is the same in both standards. Concerning responsibility and authority it should be noted that sometimes regulations require specific personnel for certain activities. The management representative should also ensure the awareness of customer requirements AND regulatory requirements - which is not required in ISO 9001:2008. Internal communication presents the same methods of action.

Management review is different in the way it adds an input for the new or revised regulatory requirements and as a consequence one of the outputs will not focus on improving the effectiveness of the quality management system processes but in maintaining their efficacy.

Management commitment	
Customer focus	
Quality policy	
Planning	Quality objectives
	Quality management system planning
Responsibility, authority and communication	Responsibility and authority
	Management representative
	Internal communication
Management review	General
	Review input
	Review output

Figure 27 - Management responsibility requirements

6.5.4 Resource management

The requirements for the resource management are presented in the next figure. The provision of resources in ISO 13485:2003 is focused in meeting regulatory, customer requirements and maintain the effectiveness of the quality system.

The management of human resources is the same in both standards but one must consider that in ISO 13485:2003 the regulations could require documented procedures for identifying training needs.

Regarding the standard for medical devices, the infrastructure includes the necessity of established documented procedures for maintenance activities when they can affect product quality. And in the work environment there are specific requirements that must be followed in order to be sure that the product quality is not affected by it.

Provision of resources	
Human resources	General
	Competence, awareness and training
Infrastructure	
Work environment	

Figure 28 - Resource management requirements

6.5.5 Product realization

The general requirements for the product realization are laid in the figure below. The planning of product realization is similar in both standard but in ISO 13485:2003 the organization shall establish documented requirements for risk management following ISO 14971:2007 as it is presented in annex 4 and 5 throughout product realization.

Regarding customer related processes, the determination of requirements related with the product are the same in both standards. The review of requirements related to the product requires that product requirements should not only be defined but also documented. In customer communication it is also necessary to add advisory notices – those are explained in the next section.

Design and development planning should be presented in documented procedures elaborated by the organization. Also besides review, verification and validation at each design and development stage, design and transfer activities must be considered. These ensure that design and design and development outputs are verified before final product specifications.

In ISO 13485:2003 design and development inputs add safety requirements according to the intended use and the outputs of risk management that should be reviewed and approved. The outputs are the same as in ISO 9001:2008 but records must be maintained.

Design and development review must include other specialized personnel but essentially this part, design and development verification, validation and control

of design and development changes are the same in both standards. In validation, there is a need for clinical evaluations and/or evaluation of performance of the medical device (annex 7).

In the purchasing process it is essential to assure that the purchased product complies with specified purchased requirements established in documented procedures. Also, for reasons of traceability the organization shall maintain relevant purchasing information for a medical product. Records of the purchased verification shall be maintained.

Regarding control of production and service provision, the general requirements are pretty similar in both standards but in ISO 13485:2003 more documented procedures are needed in implementation of labeling and mapping and work instructions. Also new requirements concerning cleanliness of product and contamination control, installation activities, servicing activities and particular requirements for sterile medical devices are given.

The general requirements of validation of processes for production and service provision in both standards are essentially the same but in ISO 13485:2003 it is necessary to establish documented procedures and maintain records of these. Also new requirements regarding sterile medical devices are added but they do not apply to OneCare Sensing. Identification and traceability are stricter in ISO 13485:2003. It demands documented procedures for identification and to distinguish from conforming product and status identification through production, storage, installation and servicing. Customer property includes intellectual property and confidential health information for medical devices. The preservation of property must include documented procedures and work instructions that include identification, handling, packaging, storage and protection.

Concerning control of monitoring and measuring devices both standard have the same approach but for ISO 13485:2003 there is a need to establish documented procedures to ensure the requirements are meet.

Planning of product realization	
Customer-related processes	Determination of requirements related to the product
	Review of requirements related with the product
	Customer communication
Design and development	Design and development planning
	Design and development inputs
	Design and development outputs
	Design and development review
	Design and development verification
	Design and development validation
	Control of design and development changes
Purchasing	Purchasing process
	Purchasing information
	Verification of purchased product
Production and service provision	Control of production and service provision
	Validation of processes for production and service provision
	Identification and traceability
	Customer property
	Preservation of property
Control of monitoring and measuring devices	

Figure 29 - Product realization requirements

6.5.6 Measurement, analysis and improvement

The requirements for the measurement, analysis and improvement are presented in the next figure. The general requirements are similar in both

standards but 13485:2003 is focused in maintaining the effectiveness of the quality management system and not improving it. Also some national or regional regulations may require documented procedures for implementation and control of statistical techniques.

Regarding the feedback of monitoring and measurement it should be implemented a procedure to provide warnings of quality problems and for input of corrective and preventive action processes which is not required in ISO 9001:2008 but it is already implemented in ISA. The internal audit and the monitoring and measurements of processes are the same in the standards. The monitoring and measurement of product is almost the same with the difference that documented procedures need to be implemented to monitor and measure the characteristics of the product.

Concerning the control of nonconforming product there must be a procedure to deal with this. In ISO 13485:2003, the organization must ensure that nonconforming product is accepted by concession only if regulatory requirements are met. Also if the product needs to be reworked, the company needs to document this procedure.

In the analysis of data ISO 13485:2003 adds the need for a documented procedure and maintain records of the results of data analysis. This could demonstrate the suitability and effectiveness of the quality system and access if improvements can be made.

There is a big difference in the standards regarding the improvement. This is the addition of advisory notices that include removals from the market, corrective actions and product recalls. The notices are issued to provide information and/or to advice on what action should be taken in the use, modification, disposal or return of a medical device. This could be added in the process of nonconforming product [78].

General	
Monitoring and measurement	Feedback
	Internal audit
	Monitoring and measurements of processes
	Monitoring and measure of products
Control of nonconforming product	
Analysis of data	
Improvement	General
	Corrective action
	Preventive action

Figure 30 - Measurement, analysis and improvement requirements

7 USA regulatory process for medical devices

In the following chapter it is is introduced the regulatory framework for the product OneCare Sensing regarding the measures necessary to market the product in the US. Since one of the objectives of ISA-Intellicare is to market the product in this country it is essential to understand the legal requirements to accomplish this.

7.1 The Food and Drugs Administration

The Food and Drugs Administration (FDA) is a scientific, regulatory and public health agency of the United States Federal Government based in Washington DC. It is responsible for protecting public health assuring the safety and performance of drugs for animal or human consumption, biological products, medical devices, foods, cosmetics and product that emit radiation. In 2014, it had a $4.4 billion budget with a staff of approximately 15000 employees comprising a lot of different areas (lawyers, chemists, physicians, microbiologists, etc) [79].

The Federal Food, Drug, and Cosmetic Act (FD&C) was passed by Congress in 1938 and its following amendments gave authority to the FDA to regulate:

- Foods
- Human Prescription and Non-prescription Drugs
- Vaccines, Blood Products and Other Biologics
- Medical Devices
- Electronic Products
- Cosmetics
- Veterinary Products
- Tobacco Products

This law was passed after the elixir sulfanilamide mass poisoning in 1937 in the United States. This disaster caused the death of more than 100 people because the elixir contained a component that is lethal to humans. Therefore a more strict regulation was needed to control the entering of new drugs in the market assuring that they were safe and effective for the users. Others cases arisen during history making amendments not only pertinent but essential to public health [79].

Figure 31 - FDA logo [80]

7.2 Process overview

In figure 32 is depicted the most pertinent USA regulatory process regarding the product OneCare Sensing. Other regulatory pathways could be followed for different products so these steps cannot be used generally for every type of medical devices.

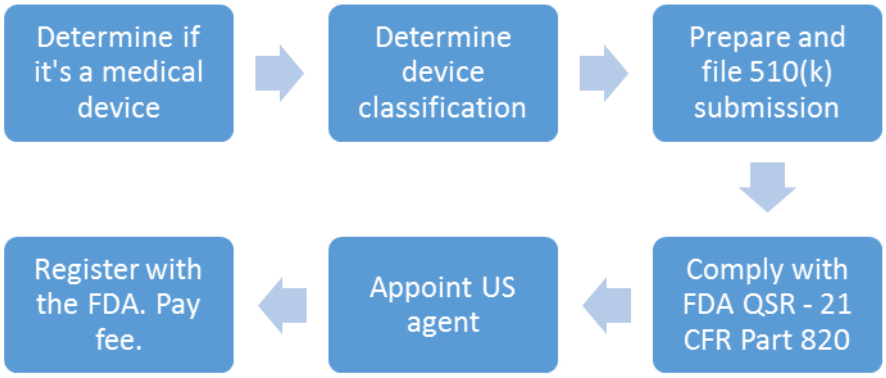

Figure 32 - Steps in FDA's Compliance Process

7.3 Determine if the product is a medical device

In section 201(h) of the FD&C [81] a medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended

purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

This definition is so vast that it tends to be obvious consider OneCare Sensing a medical device but it is essential to be sure. To do this is important to read the " Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff" issued on September 25, 2013 [82]. In this document our product is a mobile medical app since it falls under the definition of a medical device and it is intended to be used as an accessory for regulated medical devices. In chapter "V-Regulatory approach for mobile apps, section A-Mobile medical apps: Subset of mobile apps that are the focus of FDA' s regulatory oversight", the product falls under the " Mobile apps that become a regulated medical device (software) by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations. These types of mobile medical apps are similar to or perform the same function as those types of software devices that have been previously cleared or approved" . After this careful reading and analysis of appendix C-Examples of mobile medical apps of the document; OneCare Sensing is considered a mobile medical app that falls under FDA regulatory oversight.

7.4 Device classification

Device classification is made based upon the level of control necessary to assure the safety and efficacy of the device. The three risk classes that exist are:

- Class I – General Controls
    - With and without Exemptions
- Class II – Special controls in addition to general controls
    - With and without Exemptions
- Class III – Premarket Approval in addition to general controls

The classification of the device depends on three factors: intended use, the indications for use and the risks involved. The indications for use are a specific part of the intended use which is indicated in the labeling or involved during the sale of the product.

There are two ways of finding a device classification through the FDA website: searching in the classification database or by search in the device panel (medical specialty). The latest was used and the following information for OneCare Sensing was found:

Regulatory Number: 21CFR870.2910

Regulation Name: Radiofrequency physiological signal transmitter and receiver

Regulatory Class: Class II (two)

The regulatory number involves the regulation name of the device by referring to the Code of Federal Regulations Title 21, Part 870 – Cardiovascular devices, subpart C – Cardiovascular Monitoring Devices, Sec. 870.2910 Radiofrequency physiological signal transmitter and receiver. This text was revised in April 1st, 2013.

With this information it is necessary to access if our device is exempt or not. By reviewing the list of medical devices exempt provided by the FDA [83] it is concluded that devices with the regulatory number of OneCare Sensing are not exempt.

7.5 Prepare and file 510(k) submission

When someone wants to market a Class II medical device intended for human use must submit a 510(k) to the FDA unless it is exempt. There is not a template for this form but in the 21 CFR 807 subpart E, the requirements for this type of submission [84] are described. Before the marketing of the device is necessary to receive a letter from the FDA which finds the device substantially equivalent (SE) and states that the device can be marketed in the USA.

The objective of this type of submission is to show that the device to be marketed is at least as safe and effective to devices already marketed that where not subjected to PMA. Submitters must make a comparison between their device and other similar medical devices to support that they are substantially equivalent (SE). These types of devices are commonly known as the " predicate" . When the device is considered substantially equivalent by the FDA it can be marketed in the US. This consideration usually is made within 90 days based on the information provided in the 510(k). It is important to consider that the FDA does not perform 510(k) pre-clearance inspections; this means that the manufacturer should be prepared for an inspection regarding the compliance with the FDA quality system regulation (21CFR820) as from the device is cleared. The price for 510(k) Premarket notification is $2585 for 2014 since ISA-Intellicare is considered a Small Business by the FDA (has less than US$100,000,000 in sales worldwide).

A device is considered substantially equivalent if:

- It has the same intended use as the predicate and the same technological characteristics;
  Or
- It has the same intended use as the predicate and despite does not having the same technological characteristics the device does not raise new questions related to safety and performance and is at least as safe and effective as the legally marketed device.

Being substantially equivalent does not mean that the devices must be exactly identical but they must share a lot of characteristics related to safety and performance.

To search predicate devices for OneCare Sensing was used the FDA 510(k) database that contains all devices cleared under the 510(k) process. The following four devices where found that could be used as predicate:

Table 7 - Predicate devices

Device 510(k) Number	K051470	K132803	K130676	K122458
Trade/Device Name	Remote Care Management System	Medapps 2.0 Remote Patient Monitoring System, Healthpal, Healthcom, Mobile Link	Ambio Remote Health Monitoring System	Verizon Wireless Converged Health Management System
Regulation Number	21 CFR 870.2910	21 CFR 870.2910	21 CFR 870.2910	21 CFR 870.2910
Regulation Name	Physiological Signal Transmitters and Receivers	Medapps Remote Patient Monitoring System	Transmitters and Receivers, Physiological Signal, Radiofrequency	Radiofrequency Physiological Signal Transmitter And Receiver
Regulatory Class	Class II (two)	Class II (two)	Class II (two)	Class II (two)
Product Code	DRG	DRG, NBW	DRG	DRG
Dated	June 1,2005	November 12, 2013	May 13, 2013	April 6, 2013

A more intensive comparison between these systems and OneCare Sensing must be made in order to proceed with the 510(k) submission but doing this is outside the scope of this project.

7.6 Compliance with FDA QSR – 21 CFR Part 820

A quality system that helps manufacturers to achieve the applicable requirements and specifications to their products must be implemented and maintained. The FDA Quality system regulation (QSR) according with the Code of Federal Regulations (CFR) part 820 also known as current good manufacturing practices (CGMP' s) prescribes the framework for a quality system applicable to medical devices - mandatory for manufacturers that market this type of products.

Because this quality system was created before ISO 13485 the FDA does not recognize it. Also the FDA does not provide quality system compliance certificate. They only conduct random inspections to determine compliance with 21 CFR Part 820. Usually these inspections are very strict and it is necessary for a company to do periodic internal audits to assure that they are at all-time compliant.

Despite ISO 13485 is a different quality system from 21 CFR Part 820 they share about 80% of the same requirements [85]. The contents of the FDA quality system is presented below,

FDA 21 CFR 820

- Subpart A – General Provision
  - 820.1 Scope
  - 820.3 Definitions
  - 820.5 Quality System
- Subpart B – Quality System Requirements
  - 820.20 Management Responsibility
  - 820.22 Quality Audit
  - 820.25 Personnel requirements
- Subpart C – Design Control
  - 820.30 Design Controls
- Subpart D – Document Control
  - 820.40 Document Controls
  - Subpart E – Purchasing Controls
  - 820.50 Purchasing Controls
- Subpart F – Identification and Traceability
  - 820.60 Identification
  - 820.65 Traceability

- Subpart G – Production and Process Controls
    - 820.70 Production and process controls
    - 820.72 Inspection, measuring and test equipment
    - 820.75 Process Validation
- Subpart H – Acceptance Activities
    - 820.80 Receiving, in-process and finished device acceptance
    - 820.86 Acceptance status
- Subpart I – Nonconforming product
    - 820.90 Nonconforming product
- Subpart J – Corrective and Preventive Action
    - 820.100 Corrective and Preventive Action
- Subpart K – Labeling and Package Control
    - 820.120 Device Labeling
    - 820.130 Device Packaging
- Subpart L – Handling, Storage, Distribution and Installation
    - 820.140 Handling
    - 820.150 Storage
    - 820.160 Distribution
    - 820.170 Installation
- Subpart M – Records
    - 820.180 General Requirements
    - 820.181 Device Master Records
    - 820.184 Device History Records
    - 820.186 Quality System Records
    - 820.198 Complaint Files
- Subpart N – Servicing
    - 820.200 Servicing
- Subpart O – Statistical Techniques
    - 820.250 Statistical Techniques

7.7 Appoint US agent

If the company does not have local presence in the US market it is necessary to appoint a US agent as the in-country representative. This agent must either be an US resident or maintain a place of business in the US [86].

The responsibilities of this agent are to assist communication between the company and the FDA and assist the company and the FDA in setting up the random inspections for the foreign establishment. The agent does not have any responsibility related to the Medical Device Regulation or the submission of the 510(k) [86].

7.8 Register with the FDA

Companies that produce or distribute medical devices in the United States need to register annually with the FDA. This process is known as establishment registration [85].

The costs of the registration are depicted in the table below:

Table 8- Device registration costs with the FDA [87]

Year	2013	2014	2015	2016	2017
Fee	$2575	$3313	$3750	$3872	$3872

Not only a fee must be paid but it is also required by the FDA to provide a list with all the devices made, the activities performed on the devices and the premarket notification submission number. This is an electronic registration available in the FDA website [79].

7.9 Conclusion

In order to market OneCare Sensing in the USA it is necessary to follow the steps referred above. After ISA is ISO 13485:2003 certified it is recommended to create a quality plan for implementing 21 CFR Part 820. One great important part of this plan is a gap analysis that assesses where the company is and where it wants to be regarding the quality system. After this analysis a set of goals need to be established and followed to a successful implementation.

Usually this process takes 8 to 12 months depending on the company type, size and resources [85] but since the company is ISO 9001:2008 certified and will be ISO 13485:2003 certified in the near future it could only take a couple of months. The initial projected costs to market the product in this country will be $5898 in 2014.

8 Brazil regulatory process for medical devices

In the following chapter it is introduced the regulatory framework for the product OneCare Sensing regarding the measures necessary to market the product in Brazil. Since one of the objectives of ISA is to market the product in this country it is essential to understand the legal requirements to accomplish this.

8.1 Agência Nacional de Vigilância Sanitária

According to information provided by the *Agência Nacional de Vigilância Sanitária* (ANVISA) they are a "governmental regulatory agency characterized by its administrative Independence, financial autonomy, and the stability of its directors." [88] based in Brazil's capital Brasília. It is similar to the FDA in the United States and responsible for the regulation and approval of various products related with the health of Brazilians. The agency was created by Law 9782 enacted in the 26th January 1999.

Figure 33 - ANVISA logo [89]

Regarding health related services the agency is responsible for surveillance related to risk monitoring improving quality of health services. It coordinates actions nationwide carried out by states, municipalities and the Federal district. ANVISA is also responsible for formulate and enforce rules regarding health provision in hospitals, clinics and health posts [90].

8.2 Process Overview

In figure 34 is depicted the general regulatory process regarding medical devices in Brazil. The specific regulatory pathway for the product OneCare Sensing will be presented during this chapter.

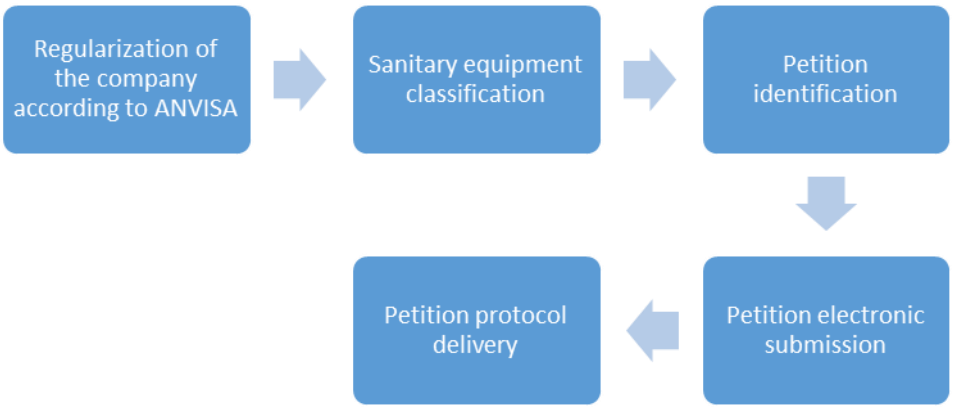

Figure 34 – Regulatory process for MD in Brazil adapted from [91]

8.3 Regularization of the company according ANVISA

This regulatory step starts with obtaining two permits:

- *Autorização de Funcionamento da Empresa* (AFE);
- *Licença de Funcionamento local* (LF).

And compliance with the Brazilian Good Manufacturing practices (BGMP). Without these two permits it is impossible to market a medical device in Brazil.

AFE

This is issued by ANVISA regarding a submission provided by a company present in Brazilian territory based in the Normative Instruction nº 01 from 30th September 1994 [92]. This means that a foreign company that wants to market their products in Brazil needs to have a subsidiary office in this country or a commercial deal with a company in Brazilian territory to assume legal liability to import their products.

LF

This one is issued by the local, federal or municipal, *Vigilância Sanitária Local* (VISA) depending in where the company is based in Brazil. These VISAs work together with ANVISA to promote the safety and security of the population. This license approves the physical installations of the company and their working staff [91].

Brazilian Good Manufacturing practices

A company that wants to manufacture, import or market medical devices in Brazil needs to comply with the BGMP established in RDC nº 59 from 27th July 2000 [93]. This is very similar to the requirements established by FDA QSR – 21 CFR Part 820. After the compliance is assured a certificate, *Certificado de Boas Práticas de Fabricação e Controle* (CBPFC) is issued by ANVISA.

Site inspections are performed every two years by ANVISA to guarantee that the company is following the requirements. In the alternating year manufacturers must make an internal audit. There are exemptions to implement by quality system but the product OneCare Sensing is not one of them - in the following sections this issue will be addressed.

8.4 Sanitary equipment classification

This classification must be made according criteria adopted by ANVISA. The type of classification of the device will determine the type of petition that must be made to the agency.

Equipment classification

Medical devices are classified in four classes depending on the risk that it has to the patient:

- Class I – Low risk;
- Class II – Medium risk;
- Class III – High risk;
- Class IV – Very high risk.

This risk classification is made by analyzing a set of 18 rules presented in the Annex II of RDC nº185/01 [94]. These rules are almost equal to the rules presented in the European directive 93/42/EEC so in a primordial analysis it is safe to assume that OneCare Sensing is a Class II device.

Economic Information Report

This report includes pricing comparisons from different markets, patient/user information, marketing materials and other materials. It is only applicable to some medical devices presented in ANVISA resolution nº3385 from 13th October 2006 [95]. The type of medical product that is OneCare Sensing, is not present in this resolution so the economic information report is not applicable.

INMETRO Certification

Some electronic medical devices need to obtain INMETRO certification in accordance to RDC no. 32 from 29th May 2011 as part of the Brazilian

registration process. The products that need this certification are presented in IN no. 08 from 29th May 2007 [96]. Again this is not applicable to OneCare Sensing since it is a medical software and it is not presented in the IN referred above.

8.5 Petition identification

There are two types of petitions to register a medical device in Brazil, *registro* or *cadastro*. *Cadastro* is a simplified registration procedure for most Class I and II devices presented in RDC no. 24/09 in which the company does not need the implementation of the BGMP. *Registro* is a more complex procedure for some Class I and II devices and all from Class III and IV in which is necessary the implementation of BGMP. According to the technical note no. 04/2012 [97] issued by ANVISA for a medical software similar to OneCare Sensing is necessary a *registro.*

According to the *registro* the following documents need to be presented by a manufacturer for a class II medical device:

- Equipment technical sheet;
- Technical file;
- Brazil Good Manufacturing Practices Certificate;
- Authorization from Brazilian registration holder;
- Free sales certificate.

The equipment technical sheet is presented in Annex II of IN 13/2009 [98]. The technical file requirements is similar to the one used by the FDA and should be prepared according to RDC 185/01 Annex III Part A/B/C and provided in Portuguese. Usually companies that already have prepared a technical file for CE marking or FDA 510(k) clearance can use the same information. A Brazil Good Manufacturing Practices Certificate is also needed to assure that the company complies with the quality system requirements. An Authorization from a Brazilian registration holder is necessary for imported equipment proving that it can import, distribute and sell products in the country. A free sales certificate is also required to prove that the product is approved for sale in your home market or a proof of marketing approval in two other countries.

8.6 Petition submission

After all the previous steps it is mandatory to submit an electronic petition of the *registro* to ANVISA. To accomplish this, first it is necessary for the company to performe its registration with the electronic system of the agency. Then one must access ANVISA website and fill the required information. There are costs associated with this process that are presented in Annex I, Item 07 from RDC no. 222, 28th December 2006 [99]. These taxes depend on the nature of the petition (*registro* or *cadastro*), if it is a simple product or a family of products, the size of the product (small, medium or large) and the size of the company (micro, small, medium or large).

8.7 Petition protocol

In the end of the process the petition needs to be physically filled in ANVISA. This is made in the *Unidade de Atendimento e Protocolo* (UNIAP) in the agency headquarters in Brasilia. The petition needs to be signed by the legal and technical company representatives. In all documents related to the product (instructions for use, labeling, etc) both signatures are needed [91].

8.8 Conclusion

In order to market OneCare Sensing in Brazil it is necessary to follow the steps referred above. After marketing of the product is approved in Europe and USA it will be fairly easy to fulfill the requirements needed in Brazil. This happens because the regulatory process in Brazil shares a lot of characteristics with the markets mentioned above despite this the process is usually more slow and complex. According to EMERGO GROUP, a regulatory medical devices consultant, the approval for marketing a class II product in Brazil could take more than 36 months because of the time needed to get the approval for the quality system certification [100].

9 Conclusion

Medical devices are only useful if they are safe and effective. It was showed that OneCare Sensing does not provide excessive risks for the users (Annex 4: Risk analysis) and its effectiveness is proven by the technology used (Annex 7: Evaluation fo clinical data). For the risk analysis the standard ISO 14971:2007 – Application of risk management to medical devices was analyzed and implemented. Clinical evaluation was compiled using guides from the European Commission. The ability to generate alarms and aggretate data from various types of sensors to be automatically accessed by the user or clinician are the main advantages of this product.

Remote patient monitoring technology presents a lot of advantages such as decrease costs associated with monitoring of chronic diseases, reducing hospital stays, deal with reduced medical staff and decrease human errors but there are still some barriers to overcome such as difficult acceptance by health care organizations and lack of awareness and education.

According to the MDD OneCare Sensing is a class IIa device with medium risk to the user. This implies the involvement of a notified body that will audit the technical documentation and quality management system in order to obtain CE marking. Following the device panel from the FDA it was showed that the product is a class II device without a 510(k) exemption. FDA will perform surprise inspections to access compliance with legal requirements related to the device. ANVISA RDC no 185/01 indicates that the medical software is a class II device and that the implementation of a specific quality management system is needed. Similarly to the FDA they also performs inspections on site.

Regarding Europe the pathway for the implementation of ISO 13485:2003 was achieved and the technical documentation to comply with the essential requirements of the directive was compiled.

In conclusion the objectives of the work were completed. The legal requirements for Europe, USA and Brazil were collected, analyzed and some implemented in ISA following the Medical Devices Directive.

9.1 Future work

The purpose of this section is to provide future work suggestions in order to fulfill the company objectives regarding the marketing of the product in different markets.

An internal audit of ISA-Intellicare regarding ISO 9001:2008 and ISO 13485:2003 should be performed in order to be sure that these quality systems are correctly implemented and being followed. After this it is recommended to have a contact with a notified body in order to obtain a CE certificate for the medical device and an ISO 13485:2003 certificate. After this the declaration of conformity must be completed and the CE mark can be affixed by the manufacturer to the product allowing its marketing in Europe. Maintain and continuous improve the quality management system is a must Then, it is recommended to implement the quality management systems and generate the documentation required to market the product in Brazil and USA. This thesis is a good guide to fulfill this objective.

In a medical devices industry survey from 2013 [1] it was showed that the growth potential in the next five years for the Asia and South American market will be huge. Japan is still the country that spends more in healthcare but soon China will become more competitive. Other countries in southeast Asia are also gaining more attention. In the same survey it was asked manufacturers in which of emerging markets they where planning to introduce a medical device for the first time. The interest in BRIC and Mexico markets is increasing since the regulatory systems are becoming more efficient. Brazil was the main answer and India came in second for small manufacturers and China for midsized and large companies suggesting a simpler and cost effective pathway in India. It is important to consider that China, US and Brazil are markets that show a lot of regulatory challenges.

Regarding the previous information it could also benefit ISA-Intellicare to understand the regulatory requirements for some Asian countries in a near future.

9.2 Summary

Although this was a very theoretical and research work it was essential to understand how a company can place a medical device in the market without safety and performance issues and following all the mandatory legal requirements. Also not having any background in the subject helped me to develop more skills such as pro activity, independency and better task management. Because the internship was in a company it showed me how a management system works and some core business aspects of the industry.

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Annexes

Annex 1: Players active in the RMT market

Annex 2: Technical File

Annex 3: CE Declaration of conformity

Annex 4: Risk analysis

Annex 5: Operational procedure – Risk management of medical devices

Annex 6: Contact of Notified Bodies

Annex 7: Evaluation of clinical data

Annex 8: ISO 9001:2008 VS ISO 13485:2003 implementation

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