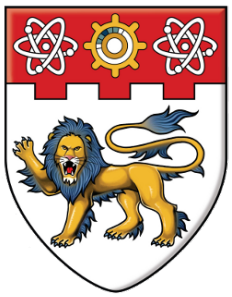

NANYANG TECHNOLOGICAL UNIVERSITY

DESIGN AND IMPLEMENTATION OF CE MEDICAL DECISION MODEL ON RESEARCH MEDICAL DEVICES

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SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

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ABSTRACT

In this Medical Technology booming era, there are many medical devices currently being researched and developed by academic institutions which are funded by grants from the various National Research Funding bodies. Many of these researchers do not come from a commercial background and are thus not aware of the regulatory requirements or processes need to be undertaken when developing such devices. There is usually a conflict between the researcher's main consideration in the development of functionality for the device as compared to the regulatory requirements needed to fulfill in order to market the device and benefit the healthcare sector.

The level of regulatory requirements needed depends on the purpose of the device and while medical grade device manufacturers may have experience in these requirements, researchers only have limited understanding in these requirements. In order to get the research device to commercialize within the time frame of the public funded research grant, the researchers have to be aware of the regulatory requirements as they progress with the development work.

With an aim to help raise the awareness of the regulatory requirements, companies with vast experience in handling the regulatory requirements in the said country are included for analysis in order to form a simple decision model that encompass the necessary requirements needed during the development work. These companies do charge a costly amount of funds in order to handle the regulations and steps are very limited in providing detailed explanation to researchers who have both limited funding and time. To assist the researchers, an overview of the related documents, standards and

components for acquiring the CE marking are described in details. These details will be used to form the basis of the CE medical decision model.

The CE medical decision model consists of six simple steps for researchers to follow during the regulatory process. The first step emphasizes on determining the applicable directive for the product. The second step looks into the safety consideration of the product design. The third step helps to classify the product based on rules and risk level. The forth step will then have the product undergo a suitable inspection tests in demonstrating compliance. The last two steps are on the documents needed to file together and the affixation of the CE marking.

The CE medical decision model is tested with three different research devices. The decision model did provide clarity in the selection of choices with a reasonable explanation. With the use of this decision model, it can help researchers in gaining a better knowledge of how the device can better fulfill the regulatory requirements before commercializing the device.

LIST OF PUBLICATIONS

Conference Presentation

1. X. J. A. Tan, J. G. K. H. Heng, K. P. Chua, & J. Y. A. Foo. “Bench to Bed: Researchers' Limited Awareness of Regulatory Requirements to Market Medical Devices”. Proceedings of The International Conference on Computer, Electronics, and Biomedical Engineering, Dubai, UAE, 2015, pp. 49-59.

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LIST OF ABBREVIATIONS

AIMD	Active Implantable Medical Device
AIMDD	Active Implantable Medical Device Directive 90/385/EEC
ASTM	American Society for Testing and Materials
CAP	Conformity Assessment Procedure
CE	Conformité Européenne (European Conformity)
CEN	Comité Européen de Normalisation (European Committee for Standardisation)
CENELEC	Comité Européen de Normalisation Électrotechnique (European Committee for Electrotechnical Standardisation)
DoC	Declaration of Conformity
EC	European Community
EC REP	European Community Authorised Representative
EEA	European Economic Area
EEC	European Economic Community
EFTA	European Free Trade Association
EN	European Norm
ERs	Essential Requirements
ETSI	European Telecommunication Standardisation Institute
EU	European Union
IEC	International Electrotechnical Commission

ISO	International Organisation for Standardisation
ITU	International Telecommunication Union
IVDMD	*In vitro* Diagnostics Medical Device
IVDMDD	*In vitro* Diagnostics Medical Device Directive 98/79/EC
MD	Medical Device
MDD	Medical Device Directive 93/42/EEC
MEDDEV	Medical Devices Guidance Document
NANDO	New Approach Notified and Designated Organisations
NB	Notified Body
NB-MED	Notified Bodies Medical Devices
NSB	National Standards Body
OJEU	Official Journal of the European Union
QMS	Quality Management System
RM	Risk Management
TDF	Technical Documentation File
TEAM-NB	European Association for Medical Devices of Notified Bodies

CHAPTER ONE

INTRODUCTION

1.1 Background

Devices for medical usage have existed more than one hundred years ago with no existence of electronic functioned medical devices. Back in era with little knowledge of using electronic means for medical purpose, mechanical device such as a simple stethoscope used for listening to the internal sounds of a human body was made purely out of a hollow wooden tube in 1816 by a French physician (Neuman, et al., 2012). After a couple of decades later, the principle of medical imaging was born was the first medical X-ray imaging device invented in 1895 and also with the aim to display the electrical signal of the heart activity, Einthoven developed a device with the use of string galvanometer, which is known as an electrocardiograph device, and later he was being honored with a Nobel Prize in 1924 (Neuman, et al., 2012). Back then, very little concern was on the regulatory compliance for these invented devices to comply with.

Moving forward to the present years, the medical devices have advanced rapidly from just the three backbone devices in the past to currently a wide range of devices which focus on areas of diagnostic, monitoring and also treatment of diseases or condition that affects everyone. Medical devices with the use of technology have covered the different aspects of healthcare ranging from a simple daily home object, such a handy plaster or an alcohol swab, to a more sophisticated medical equipment used in hospitals, like Computed Tomography (CT) scan machine, hemodialysis machines or magnetic resonance imaging (MRI) machines (Ciruana, 2014).

With the increasing development work in medical devices, newer developed devices offer better-quality diagnostics and treatment alternatives to tackle the vast diseases, infections and also aging population issues (Simoens, 2008) but so does the potential risks involved in the new devices when recently a large scale of recalls are executed on implantable devices and surgical devices (Kramer, Xu, & Kesselheim, 2012). In order to minimized the risk of the healthcare workers or consumers in using malfunctioned medical devices, regulatory compliance organizations are formed in every country to regulate the issues on safety, quality and performance.

For any medical device developer to place a medical device on to the market shelves for sale, the product has to undergo a regulatory process required by the regulated authority of the any country (Cevc, 2013). This process is known to be both expensive, tedious and time consuming which generally requires a considerable amount of funding. While this may be apparent to the seasoned medical grade device manufacturers, researchers developing a novel electronics-based device using public-funded research grants may have limited knowledge on such regulatory requirements. Generally, only approved medical devices can be marketed to the healthcare industry which then can initiate the recovery of the development costs before it can generate any revenues (Tan, Heng, Chua, & Foo, 2015).

With this issue in mind in the worldwide medical technology sector, globalized companies, such as Biosensors, Baxter, Becton Dickinson, etc, and Singapore's start-up companies, such as, HealthSTATS, Veredus Laboratories, etc, are not only focusing on research and development field such as product development but also addressing the regulatory issues (Economic Development Board (EDB), 2015). While seasoned

companies are able to handle the regulatory issues, local startups such as Endomaster, SynPhNe and HistoIndex will face a funding difficulty in keeping up the regulatory issues while developing the intended product. In the mind of every researcher, the ultimate goal for developing a medical device is to help improve patients' quality of life through diagnosis, treatment or medication. However, it is apparent that there is a knowledge gap pertaining to the regulatory requirements for most researchers about the reality of bringing their ideas to become a marketed medical device so to benefit the intended users (Tan, Heng, Chua, & Foo, 2015). One of the research institution, Nanyang Technology Univeristy (NTU), makes a pro-active decision in starting a innovation company, NTUitive Pte Ltd, to help researchers in bringing the invention from laboratories to marketplace. Although with the assistance of NTUitive, it will still be costly and time consuming for researchers to commercialized their product if they do not include the concurrent preparation for the regulatory issues of the selected country.

The United States and the European Union (EU) are one of the largest and most lucrative market for researchers to have their developed devices sold in. Article (Basu & Hassenplug, 2012) and press release (MedTech Europe, 2010)have been showing the comparison of United States and EU in terms of regulatory procedures and the timing to market the product. Appendix A1 also shows the time difference between the EU and US for the patients to access the medical technology of various medical device companies. In this thesis, the selected country will be the EU as it is formed up by a number of countries which for researchers will seem to be a lot more beneficial to have their developed products acknowledged in the medical device field.

European Union

The forming of European Union (EU) dated all the way back to 1957 where the Treaty of Rome was signed. The EU underwent a few treaties which previously were named as European Economic Community (EEC) during the Rome Treaty in 1957 and European Community (EC) during the Maastricht Treaty in 1992. The most recent treaty, Treaty of Lisbon, was signed by the EU member states in 2007 and officially forms the basis of EU (European Union, 2015a).

Table 1 - Member States in EU

Year of Entry into EU	Member States of EU	No of Countries
1952	Belgium, France, Germany, Italy, Luxembourg, Netherlands	6
1973	Denmark, Ireland, United Kingdom	3
1981	Greece	1
1986	Portugal, Spain	2
1995	Austria, Finland, Sweden	3
2004	Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia	10
2007	Bulgaria, Romania	2
2013	Croatia	1

The EU is formed up by 28 member states with Croatia being the most recent member and has a total population of more than 500 million as of 2014 (European Union, 2015b). Table 1 shows the formation of the EU with the involved member states. The European Economic Area (EEA) was founded at beginning of 1994 and had a contract

and understanding between the EU and the member states of the European Free Trade Association (ETFA).

EEA promotes free movements of goods, personnel, services-related and capital throughout the 27 of 28 member states of EU and three of four member states in ETFA. Currently Croatia is the only member state in EU to be provisionally participating in EEA. ETFA was established in the middle of 1960 with the aim of providing free trade in member states that were not able to join under the EEA. As of 2014, the ETFA members consist of four European countries (Iceland, Liechtenstein, Norway and Switzerland). Figure 1 shows the European countries that are under EEA and EFTA.

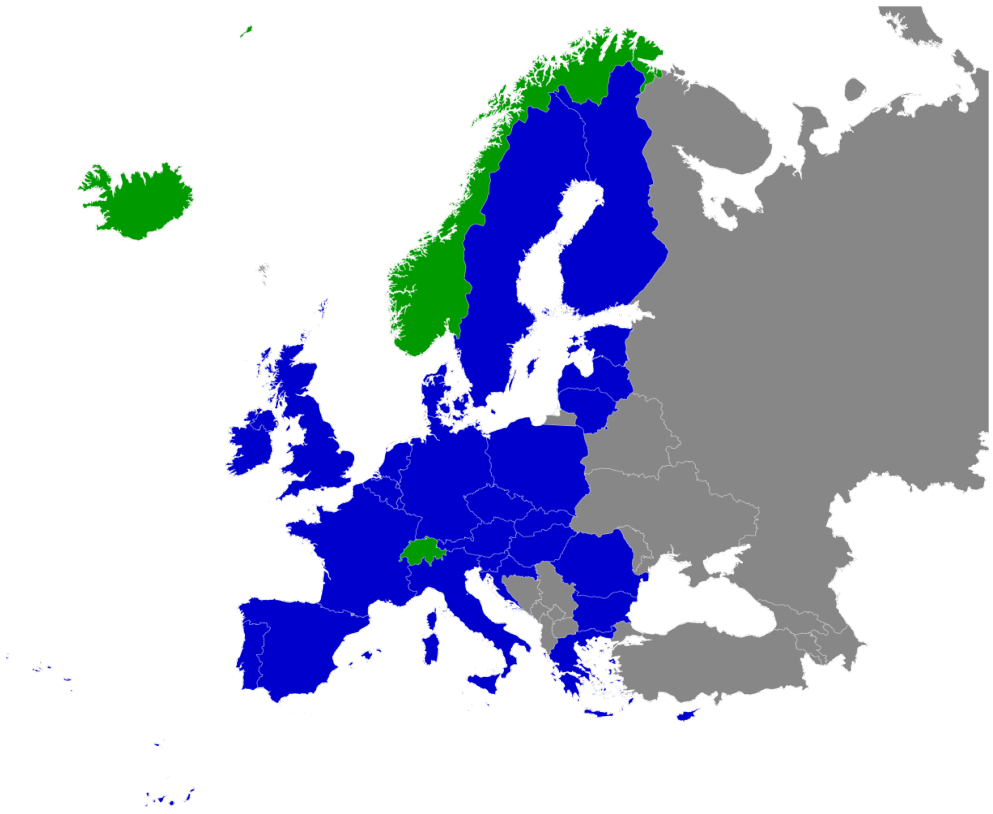


Figure 1 - Countries under EEA (Blue) and EFTA (Green)

The creation of EU legislation comprises the involvement of three institutions which are the European Commission, the Council of European Union and the European Parliament. Basically the European Commission serves for the interests of the union, the Council of European Union serves as the government of the individual countries and the European Parliament serves as the speaker for all EU citizens. The EU legislation comprises of regulations, directives and decisions (European Union, 2015c).

Regulations

An EU regulation is a mandatory legislative act that all the member states of EU must adhere to. It does require the need to convert to national legislation. For example, when dealing with similar matters in regards to trading policy, the EU regulations has the authority to override all national legislations.

Directives

A directive is a legislative act that requires all the member states of EU to completely fulfil the defined requirements. The individual member state has the decision-making power on the procedures needed to fulfil the defined requirements and thus include into its national legislation. There are a whole lot of directives that can be found on the European Commission website but the directives related to all medical devices will be discussed further in Chapter 3.

Decisions

A decision is mainly applicable to a specific EU member state or the individual company while not affecting other member states.

CE Marking

The initials 'CE' comes from the French term, Conformité Européenne, which translate to 'European Conformity'. The CE mark has been in existence since 1993 and is a legal compulsory requirement for products intended for sale within the EEA and EFTA (European Commission, 2011). A CE marking is a form of indication that a product fulfills with all the relevant and necessary requirements and has been subjected according to the selected conformity assessment option(s) of the applicable European Directives (European Commission, 2015a).

Consumers, without proper knowledge on CE marking, may falsely assume that CE marking is a quality symbol, a marketing tool or an indicator that a product was made in Europe. The purpose of the CE marking is to grant manufacturers the rights in placing products and make sure the free movement of goods on the EU market. In fact, it merely states that the product is evaluated and fulfilled the legislative requirements before placing on the market (European Commission, 2011). By affixing the CE marking on a product, the manufacturer declares that their developed product does conform to respective directives and standards (European Commission, 2015a). The manufacturer bears the responsibilities of the CE marking and therefore ensuring the product's validity to be sold throughout the EEA.

However not all products require to bear the CE marking, but in this case, it is a legal mandatory requirement for medical devices to be affixed with CE marking. Figure 2 shows the CE marking logo and Figure 3 shows an example of the labelled CE marking on the product.

Figure 2: CE marking Logo

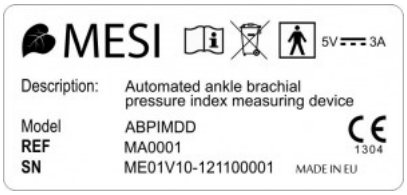


Figure 3 - Example of CE mark labelled on the back of the product

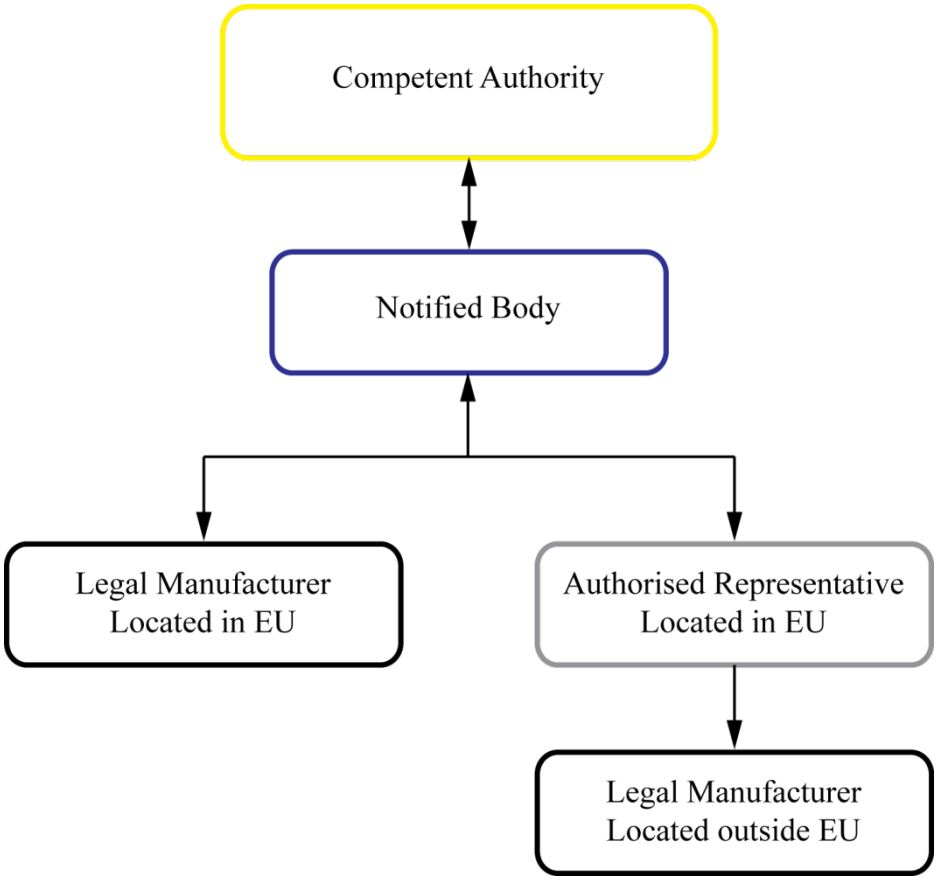


Figure 4 - Relation between Key Players in EU

Competent Authority

The government of each member states of the EU will have to entrust and appoint a competent authority with the power of executing the legal rights in controlling the usage and sales of the medical devices. The competent authority has to ensure the compliance with lawful requirements is met accordingly for the manufactured medical devices before it can be on the EU market (Teysseyre, 2013). The roles and responsibilities of the competent authority are to examine the notified bodies (NBs), oversee the EU market and ensure the EU directives transposed into the national law. MHRA (Medicines & Healthcare products Regulatory Agency) is one of the well-known competent authorities that oversee all medical devices in the United Kingdom. The rest of the respective competent authorities for each country in EU are included in Appendix A2.

Notified Body (NB)

A notified body is a certification organization assigned by respective member states in the EU to carry out conformity tasks stated in the annexes of the directives. NB is responsible for issuing CE marking certificate to manufacturers whose manufactured products conform to the essential criteria stated in the annexes of respective directives (Teysseyre, 2013).

A list of the notified bodies with updated information can be found on New Approach Notified and Designated Organizations (NANDO) website. It will provide information such as the identification number of NBs and the assessment of directives by NBs. Appendix A3 has a list of notified bodies.

European Community Authorized Representative (EC REP)

Products that are not developed within one of the member states of EU, usually requires a European Community Authorized Representative to be appointed by the manufacturer in the assistance of selling the products in Europe. The definition of EC REP is clearly stated in Article 1 for all medical devices directives. The EC REP can be any legal company or person appointed by the manufacturer and will be tasked to handle doubting issues or reviews by the competent authorities or notified bodies (Teysseyre, 2013). The logo of EC REP has to be labelled on the products or packaging with the details of the EC REP such as name and address. Mainly the manufacturer still holds the responsibility for any actions performed by the EC REP. The logo of an EC Rep is shown is Figure 5.

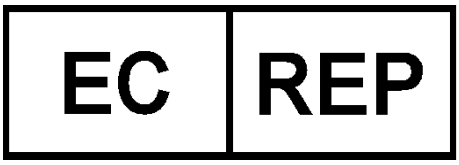


Figure 5 - European Community Authorized Representative (EC REP) logo

Manufacturer

The manufacturer (which maybe the researcher) is responsible in regards to the whole process from design and development to labelling of the device before selling in the EU market. The definition of a legal manufacturer can be found under Article 1 of all medical related directives. After developing the product and testing, the legal manufacturer also has to search for notified bodies, authorized representative and lastly

attaching the CE marking onto the device. The legal manufacturer also has the obligation to make sure that the products fulfilled all the necessary requirements and thus showing conformity in the declaration of conformity (DoC) (Teysseyre, 2013).

1.2 Objectives

While marketing a medical device according to the regulatory requirements may be well-understood by medical grade device manufacturers but for researchers, they usually have limited understanding of such requirements or procedures. It is also becoming increasingly common that providers of research grants derived from public funds are expecting the grant awardees, especially researchers focusing on device development, to bring their end product from bench to bed or product commercialization. Hence, the objectives of this thesis are to:

1) Cover the general approval process of different companies for different types of medical related devices.
2) Detail the considerations to market developed products in well regulated EU countries.
3) To bring together a decision model for the medical devices to be regulated in EU countries.

1.3 Scope

The thesis is organized into the following six chapters:

Chapter 1 covers the motivation for the realization of this thesis. This chapter includes the background of medical devices, the problem faced by researchers and developers, a brief introductory on EU and CE marking and lastly the objectives of this thesis.

Chapter 2 will be covering on the various companies in and out of Europe that provides recommended steps in order to handle the regulatory issues on getting the CE marking. These companies ranges from private companies all the way to a government department that handles import and export. This chapter shows that the recommended steps vary across the companies be it a European company or not.

Chapter 3 will be briefly touching on the relevant medical directives that are available in the EU and the overview of the different standards available. This chapter explains on how the directives came about and the definitions for the different groups of medical related devices. This chapter also covers an introductory explanation on the different types of standards available from national to international and the two widely used international standards that focus on managing the quality and risk for medical devices.

Chapter 4 focuses on the forming of the CE medical decision model that will be an assistance tool for researchers to refer to while developing and preparing to commercialized their medical invention. The CE medical decision tool is a formation by combining the building blocks, such as classification, conformity assessment options, etc., and the various steps from Chapter 2. The CE medical decision tool is a

simple six steps procedure intended for researchers to include in their commercializing process.

Chapter 5 is on the demonstration of the CE medical decision tool on various developed devices by research institution and institute of higher learning. There will be three different devices that CE medical decision model will be used on: an accessory for wheelchair, a stroke rehabilitation system and a diagnostic device for peripheral arterial disease.

Chapter 6 will be on the discussion of the case studies with the application of the CE medical decision model. Finally, the future works that can be carried on will be recommended.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Starting from 15 June 1998, all kinds of medical devices that are sold in EU market must conform to the given requirements in the medical related directives and also getting certified with a CE marking when selling or using the devices within European Union (Schoenmakers, 1998). In this chapter, the CE marking steps by various companies from Europe and United States will be introduced and briefly explained.

2.2 CE Marking Steps by Companies in Europe

2.2.1 LNE/G-MED America

With a history since 1901, the Laboratoire National d'Essais (LNE) was established in France and set up to meet industrial testing and measurement requirements (LNE, 2010). In 1978, LNE changed its legal status and became stated-owned enterprise attached to the French Ministry of Industry. In 2005, LNE opened a subsidiary in North America known as LNE/G-MED America. LNE has officially renamed as the Laboratoire National de Métrologie et d'Essais and is the leading notified body (NB 0459) in France. LNE/G-MED issues certificates for all conformity procedures under the three medical device directives (LNE, 2010).

In order to achieve CE marking for AIMDs, MDs and IVDMDs, it requires serious planning on the procedures. LNE/G-MED America provided a possible way known as 5 Key Stages of CE Marking (LNE/G-MED America, 2011) for manufacturers to

follow and it will be briefly elaborated. The full details o the CE marking procedures for MDs, AIMDs and IVDMDs are shown in Appendix B1.

Stage 1: Confirmation of Medical Device Status and Class/ Category

a) Manufacturers must identify the applicable EU directives with reference to:
    - AIMDs (90/385/EEC with amendment of 2007/47/EC)
    - MDs (93/42/EEC with amendment of 2007/47/EC)
    - IVDMDs (98/79/EC)
b) Using the rules stated in Annexes and Articles of the applicable directive, further place the device into its class/ category according to the risk level:
    - AIMDs (Risk level similar to Class III devices in MDD)
    - MDs (Class I (Low), IIa & IIb (Moderate), III (High))
    - IVDMDs (List A, List B, Self-tesing and General IVDMDs)

Stage 2: Identifying and Meeting the Essential Requirements

- According to the regulations in EU, the medical device has to be checked and confirmed suitable and demonstrate compliance to the essential requirements stated in the respective directive (Annex I).

Stage 3: Technical Documentation

In order to fulfill the requirements from the applicable harmonized standards, the following details have to be included (LNE/G-MED America, 2011):

a) A descriptive information of the product and list of specifications
b) Information regarding the manufacturing procedure
c) Risk Management (RM) file
d) Verification of the product design and confirmation of test reports
e) Clinical assessment being evaluated
f) Labeling of the CE marking and other symbols (safety, etc.)

Stage 4: Conformity Assessment Options

- Having the product gone through the classification/ categorization in Stage 1b, the class/ category will then help to determine the conformity assessment options available for the manufacturer to undergo in order to obtain the CE marking. The available conformity assessment options are (LNE/G-MED America, 2011):
  a) Full Quality Assurance System
  b) Type/ Design Examination
  c) EC Verification
  d) Quality Assurance System for Production
  e) Quality Assurance System for Product (Not applicable to AIMDs & IVDMDs)
  f) Declaration of Conformity
  g) Batch Release (Only applicable to IVDMDs)

  The chosen assessment option will subsequently affect the complexness of the process during assessment.

Stage 5: Declaration of Conformity

- It is a necessary declaration that is done by the manufacturer with the affirmation of the intended device does fulfill all the applicable essential requirements (LNE/G-MED America, 2011). It is also to confirmed that the device indeed went through the suitable conformity assessment option (stated in the Annexes) and is verified in terms of the design, manufacturing procedure and also examined. The declaration of conformity will be part of the technical document prepared in Stage 3.

2.2.2 SGS (Société Générale de Surveillance)

SGS was established in 1878 and subsequently in 1919, the company registered itself in Geneva (Switzerland) with its name as Société Générale de Surveillance (SGS Group Management SA, 2014a). SGS is one of the world leading company with the capabilities to perform inspection, testing, certification and also verification. SGS focuses on many industrial areas such as Energy, Industrial Manufacturing, Life Sciences, etc. and provides services such as auditing, certifying, consultancy, inspection, testing and verification which are indeed crucial in getting the CE marking (SGS Group Management SA, 2014b).

The company has a vast experience in the getting products into the European market given that it has a few notified bodies like SGS UK (NB 0120), SGS Finland (NB 0598), SGS Belgium (NB 1639) and SGS Hungary (NB 1979). It has also been

accredited by the United Kingdom Accreditation Service (UKAS) to perform auditing on the quality management system ISO 13485. SGS uses its experience and expertise in formulating the steps required for the CE marking process (SGS Group Management SA, 2012) and the details of the steps can be found in Appendix B2.

Step 1: Identification of the applicable directive(s) for the product

- Available directives for medical related devices: AIMDD, MDD or IVDMDD

Step 2: Select the conformity assessment procedure relevant to the applicable directive

a) For AIMDD, select one or combining two different Annexes (Annex 2 to 5)
b) For MDD, select one or combining two different Annexes (Annex II to VII)
c) For IVDMDD, select one or combining two different Annexes (Annex III to VI)

Step 3: Verify and use any applicable harmonized standards

- Harmonized standards are not a must but it is useful to assist manufacturers in the quality systems compliance and risk management. Examples of harmonized standards are EN ISO 13485 and EN ISO 14971which focuses on quality systems compliance and risk management.

Step 4: *Notified body requirement*

a) According to AIMDD 90/385/EEC, it is a requirement for the manufacturer to find a notified body as AIMDs are considered as high risk
b) According to MDD 94/42/EEC, Class I (sterile, measuring function) to Class III requires a notified body
c) According to IVDMDD 98/79/EC, all of the *in vitro* diagnostic devices with the exception of general IVDs, does require the notified body

Step 5: *Make sure that the product complies with the essential requirements*

- It is a must to comply with the requirements stated in the respective directive. Annex 1/ I have stated the requirements necessary for manufacturers to refer to and comply with.

Step 6: *Preparation of technical documents*

a) For all AIMDs, manufacturers have to prepare a technical documentation with compliance to the essential requirements stated in the Annex 1 of AIMDD. Additional documentation such as clinical evaluation and risk management are compulsory in the technical documentation.
b) For all MDs, manufacturers have to prepare a technical documentation with compliance to the corresponding requirements stated in the Annex I of MDD and also include clinical evaluation and risk management.

c) For all IVDMDs, manufacturers have to prepare a technical documentation with compliance to the corresponding requirements stated in the Annex I of IVDMDD and also include clinical evaluation and risk management.

Step 7: Certifying of the quality management system and examining of technical documentation by the notified body (when deemed necessary)

a) According to AIMDD, the technical documentation will have to be evaluated by a notified body with references to either Annex 2 (focus on EC design) or Annex 3 (focus on EC type)
b) According to MDD, the technical documentation will have to be evaluated by a notified body (not necessary for Class I MDs) with references to either one of the Annexes (II focus on a full scale quality check, III focus on EC type, IV focus on verification, V focus on the quality of the production, VI focus on the quality of the product).
c) According to IVDMDD for general IVDs to List B IVDs, the technical documentation will have to be evaluated by a notified body with references to either one of the Annexes (V focus on EC type, VI focus on verification, VII focus on the quality of the production). The List A IVDs requires a particularly detailed design dossier with the inclusion of device design criteria in Annex IV (focus on full scale quality check).

Step 8: Provide the relevant accompanying documents and declaration of conformity (DoC)

- The manufacturer has to prepare the declaration of conformity (DoC) with the inclusion of the accompanying documents of the certificates, either technical documents or design dossier, etc.

Step 9: Thorough look up on any existing applicable requirements

Step 10: Attach the product with the CE marking symbol

2.2.3 TÜV Rheinland

TÜV (Technischer Überwachungs-Verein) translate in English means Technical Inspection Association, works to validate the safety of all kinds of products. TÜV Rheinland Group is founded in 1872 and based in Cologne, Germany (TÜV Rheinland, 2015a). The company has been in the forefront as a worldwide provider for technical, safety and certification services. TÜV Rheinland focus on six main business direction which are Mobility, Products, Industrial Services, Life care, Training & Consulting and lastly Systems (TÜV Rheinland, 2015a). Medical device certification can be obtained through TÜV Rheinland with the assurance that the product or device does meet all the appropriate safety standards. TÜV Rheinland also do perform conformity assessments to all European medical device directives that are required for obtaining the CE marking (TÜV Rheinland, 2015b). Appendix B3 shows the proven steps that can help manufacturers in obtaining the CE marking.

The TÜV Rheinland Group have two notified bodies (NB 0197 in Germany, NB 1936 in Italy) to assist manufacturer in their conformity assessment procedures. Given the advantage of having two notified bodies in different parts of Europe, TÜV Rheinland Group has come out with a simple six steps for manufacturers to gain their CE marking (TÜV Rheinland of North America, 2014).

Step 1: Check the meaning of the different medical device with its purpose

- The manufacturer has to check on the suitable definition with its purpose that fits the intended product and subsequently decide on the suitable directives for the product (MDD, AIMDD or IVDMDD).

Step 2: Classify/ categorize the intended device

a) With reference to MD directive, all intended devices are being classified according to the rules predefined in Annex IX.
b) With reference to AIMD directive, all intended devices that are both active and implantable does not require any form of classification.
c) With reference to IVD directive, all intended devices that are for *in vitro* purpose are distinguished according to self-testing devices, List A devices, List B devices and finally the general IVDs for any devices that does not belong to the previous three categories.

Step 3: Determine the applicable conformity assessment options with/ without the need of notified body

- After the classification or categorization of the manufactured device, notified body is needed to assess the examination s based on the respective directives and also audit on the Quality Management System. It is a necessary condition to involve the NB for AIMDs. Both IVDMDs and MDs requires the engagement of a NB with the exception of Class I (no measuring function and non sterile) and general IVDMDs.

Step 4: Preparation of technical documents of the intended device

- It is an obligation for the manufacturer of all classes/ categories medical devices to organize and do up a technical documentation with the inclusion of the following content:
  a) Description of device
  b) Technical design documents
  c) Harmonized or international standards applied
  d) Explanation of chosen solutions to conform to the requirements
  e) Analyzed result for risk assessment
  f) Clinical evaluation
  g) Labeling and instructions for use
  h) Validation of certificates

Step 5: Examination (EC Type or Design) to be applied on the intended device

- The manufacturer has to decide between EC Type examination procedure and product design documentation procedure for all AIMDs, Class II (a & b) and List A IVDs devices. A selected notified body of the TÜV Rheinland group will test either the device or look through the design dossier. TÜV Rheinland will then issue a certification in accordance with the corresponding directive upon successful inspection.

Step 6: Implementation of conformity assessment procedure

- Most manufacturers choose to have their quality management systems being audited. The manufacturers can also have an alternate path to the inspection by choosing the procedure for verification in terms of samples or individual tests with reference to the Annexes in MDD and IVDMDD. The notified body will subsequently award an authorization for the CE marking upon a successful completion of the conformity assessment procedure.

2.2.4 Medical Device Certification GmbH

Medical Device Certification GmbH also known as MDC GmbH was founded in 1994 in Germany (MDC GmbH, 2014) and is recognized under the list of notified bodies for the MDD 93/42/EEC. MDC GmbH is both a notified body (NB 0483) for medical devices and a certification body for services like performing audits and certifying quality systems according to international standards the can recognized in CE marking

for the medical related devices. Being a notified body for medical devices, MDC GmbH is able to perform conformity assessments on MDD (MDC GmbH, 2009) and IVDMDD (MDC GmbH, 2006) only.

With the past 20 years of experience in both MDs and IVDMDs, MDC GmbH has formulated and provided 8 steps for potential manufacturers to look into when planning to gain the CE marking. The 8 steps are applicable for both MDs and IVDs medical device directives. The full details on the steps are found Appendix B4.

Step 1: Decision on device covered under directives

- The manufacturer has to make a decision on the intended use of the designed product to be a medical related device or not and also to make sure that the designed product is being covered in one of the three medical device directives.

Step 2: Classification/ categorization of device

a) In Annex IX of MDD contains the classification rules (a total of 18 rules) for the device to be classified as Class I, IIa, IIb or III device.
b) In Annex II of IVDMDD contains the categorization of products which are List A, List B, self-testing and other general IVDMDs.

Step 3: *Selection of notified body*

- The manufacturer has to find a suitable notified body from a list which suits the selected directive. During the search, conversation and information exchanging will be done with the notified bodies.

Step 4: *Decide on the conformity assessment route to perform*

a) After the classification has been done, the manufacturer will have to further decide on the conformity assessment route which is suitable for the device (MDD Annex II to VII).

b) After the categorization has been done, the manufacturer will have to further decide on the conformity assessment route which is suitable for the device (IVDMDD Annex III to VII).

Step 5: *Preparation of technical files/ design dossiers*

- The technical files are required for device of all Classes and Categories of medical devices. It has to include the declaration of conformity by the manufacturer, a overall explanation of the device, manufacturing methods, results gotten from risk analysis and calculations, clinical evidence, etc.

Step 6: *Submitting of prepared technical files to and examined by selected NB*

- The technical files of the medical device will then be inspected by the selected NB from Step 3.

Step 7: Review and inspection of production operation

- Audit checks will be done on the production line before any certifications can be awarded to the manufacturer for the display of compliance according to the examination in the Annexes.

Step 8: Awarding of relevant certification

- Relevant certificates will be issued according to the examination that has been performed on the intended device. The certificates will have to be renewed every five years.

2.2.5 British Standards Institution Group

The British Standards Institution (BSI) Group was founded in 1901 in London, United Kingdom. The group as a private company subsequently was awarded the Royal Charter in 1929 and adopting the name BSI in 1931 (BSI Group, 2015). The BSI group core focus is on providing, developing and amending standards. It also does provide a wide-range of training courses, management systems examination and certifications related for testing (BSI Group, 2015).

BSI group is one of the world leading certifying body for auditing and certifying of companies that meet the management system standards. It also has two notified bodies (NB 0086 & NB 0535) that helps manufacturer in the compliance of medical related directives. With a vast experience in development of standards and operations in over

170 countries worldwide, BSI group has created a simple guide for manufacturers to adhere accordingly in order to obtaining the CE marking and it is a 5 steps procedure for CE marking (BSI Product Services, 2010) and is also shown in Appendix B5.

Step 1: Classification of your medical device

- The device has to properly conform to one of the three medical related directives with it definition and intended usage clearly defined. Based on the selected directive, then will the classification or categorization take place to clearly specified the risk of the device either according to the rules (Rule 1 to 18) or groupings.

Step 2: Identifying and meeting essential requirement

- All device that bears the CE marking have to fulfill the relevant essential requirements as they are cover the safety aspects, risk/ hazards analysis, transportation and storage, etc.

Step 3: Preparing technical documentation

- It is a requirement for the technical documentation to be done for all device classifications/ categorizations without being affected by the decision of Annexes. It has to contain information such as demonstration of conformity with essential requirements, product specifications and information about the

manufacturing procedures. The complexity of the device will determine the scope and detail level of the technical document.

Step 4: *Completing required conformity assessments*

- With the dependency of the classification or categorization of the device, a set of conformity assessment modules are available to help to achieve the CE marking. Either one or a combination of two Annexes will be performed to achieve the CE marking.

Step 5: *Signing a Declaration of Conformity*

- Once the process for CE marking is done, the declaration of conformity has to include:
    - Meet the relevant essential requirements
    - Appropriate conformity assessment procedures have been completed
    - Device designed, manufactured and tested in accordance with technical documentation

2.3 CE Marking Steps by Companies in United States

2.3.1 International Trade Administration

International Trade Administration (ITA) is under the Department of Commerce with its aim to strengthen the US industry while include promoting trade and investment both external and internal and also ensuring an impartial trading with compliance

according to the trade legislation (International Trade Administration, 2015). ITA focuses on three business sections: Global Markets, Industry and Analysis, Enforcement and Compliance. These three units help to maintain the investments, development of international trading and also enforcing the trade legislation and compliance (Department of Commerce, 2015).

With the expertise in the field of trading and compliance, it deals with exporting goods out of US into various countries and region which includes Europe. The ITA then provided a guide for US manufacturers to use and it is known as CE marking in 8 Steps (Mohr, 2011) and is shown in Appendix B6.

Step 1: Definition of the product

- According to the definition stated in the medical related directives, the product has to match the definition on whether it is a MD, AIMD or IVDMD.

Step 2: Classification/ Categorization

- Medical devices of different intended purpose fall into various risk classes or categories (MDs, AIMDs and IVDMDs). For MDs related, there are four risk classes available: Class I (low risk), II (a & b) and III (high risk). For AIMDs related, there is only one single risk class (high risk). For IVDMDs related, there are four categories available: general IVDs, self-testing IVDs, List A IVDs and List B IVDs.

Step 3: Meet essential requirements

- The purpose for the essential requirements are for the protection of health and safety and they are set out in general terms. It covers both risks and hazards that are likely to occur during design phase, production phase and handling phase. The essential requirements can be found in Annex 1/ I of the respective medical directives. The compliance with harmonized standards also provide a form of conformity with the corresponding requirements stated in Annex 1/I.

Step 4: Follow a conformity assessment procedures (CAP)

a) The selection of the conformity assessment route is decided based on classification or categorization of the device. Low risk devices like Class I MDs, the conformity assessment procedure can be a self-certification. For higher risk devices (Class IIa MDs to IVDs), the conformity assessment requires the notified body to conduct the assessment.

b) The use of the services from a notified body is applicable to all AIMDs, certain IVDMDs and MD (Class IIa and above). The notified bodies are accredited test laboratories based in EU countries. The notified body will make the final assessment of the conformity with the respective directive and award a certificate.

Step 5: *Assemble the technical documentation*

- The technical documentation has to include all relevant information to demonstrate compliance with the requirements stated in the directive.

Step 6: *Affix CE-marking*

- The CE marking symbol has to be placed on both the device and any accompany documents (e.g. instruction of use). This symbol will show that the manufactured device complies with the applied directive. If a notified body is selected, the notified body's number has to be together with the CE marking.

Step 7: *Do up a Declaration of Conformity*

- It is an important requirement for all medical grade devices to have a declaration of conformity being declared. It is a single page document and contains the declaration of the manufacturer to demonstrate conformity to the requirements stated in the directive.

Step 8: *Appoint an Authorized Representative*

- Outside of Europe manufacturers have to choose and hire an authorized representative located in one of the EU countries. This appointed authorized representative will then be the main link between the competent authorities and the overseas manufacturer.

2.3.2 Emergo Group Inc

Emergo was established in 1997 to assist United States (US) medical device companies in exporting products to Europe. Emergo has grown to be a leading worldwide consultancy in medical device and *in vitro* medical device. The company provides a widespread range of compliance and market access services such as registration of device, compliance in quality management system, representative in EU countries, consultation in regulatory issues, qualifications necessary for distributors and lastly reimbursements (Emergo Group Inc, 2015a). Emergo also has more than fifteen years of experience in assisting small medical device companies and IVD manufacturers in obtaining CE marking in Europe. Emergo has formulated its own preferred steps according to the vast experiences gained from the preparation of AIMDs, MDs (Emergo Group Inc, 2015b) and IVDMDs (Emergo Group Inc, 2015c) in obtaining the CE marking. Appendix B7 shows the steps for all the three medical devices (AIMDs, MDs and IVDMDs).

Step 1: Identify which EU medical device directives is appropriate for the product

a) 90/385/EEC: AIMDD (active implantable related)
b) 93/42/EEC: MDD (general)
c) 98/79/EC: IVDMDD (*in vitro* diagnostic related)

Step 2: Decide the class/ category of the device according to applicable directive

a) If MDD is applicable, classify the device in accordance to Annex IX
    - Low risk: Class I, I (Sterile), I (Measuring)
    - Medium risk: Class IIa
    - High risk: Class IIb
    - Highest risk: Class III
b) If AIMDD is applicable, classify the device of equivalent risk level as Class III MDs
c) If IVDD is applicable, categorize the device in accordance to Annex II
    - General IVDs (self certified)
    - Self-testing IVDs (exclude devices from List A and List B)
    - List B IVDs (found in Annex II)
    - List A IVDs (found in Annex II)

Step 3: Implementation of Quality Management System (QMS)

Most commonly used standard to achieve QMS compliance will be ISO 13485 standard.

a) In MDD and AIMDD, medical devices excluding Class I (non-measuring, non-sterile) devices are to follow Annex II or V of the respective directives
b) In IVDMDD, all *in vitro* devices excluding general IVDMDs are to follow Annex VII

Step 4: Preparation of Technical Files/ Design Dossier in accordance to Class/ Category

a) For Class I to IIb medical devices and general IVDs to List B IVDs, the preparation of a Technical File is required and it must include information regarding the device with demonstration of compliance according to the respective directives
b) For Class III medical devices, AIMDs and List A IVDs, a preparation in the Design Dossier is required and a must to include clinical data

Step 5: Assign an Authorized Representative

- The manufacturer who is located outside of EU countries, has to appoint an authorized representative which is stationed in the EU countries to assist with the regulatory issues when necessary.

Step 6: Audit Technical Document/ Design Dossier

- Medical devices (inclusive of Class I measuring function and sterile) and general IVDMDs are required to present the prepared technical files/ design dossier to be reviewed and examined by a notified body.

Step 7: Issued of ISO 13485 and CE marking certificates

- After a successful audit check has been performed on both the device and the quality management system, certificates will be issued based on the relevant

audit (e.g. ISO 13485 certificate will be awarded if the audit check for the facility management is approved). It is required to renew the ISO 13485 certificate yearly.

Step 8: Registration with Competent Authority (All Class I and IVDMDs)

- All Class I (Is, Im) and IVD medical devices have to do a registration with the European Competent Authority (Ministry of Health) where the Authorized Representative is located in. Registering for Class IIa, IIb and III medical devices are not required by most of the EU countries.

Step 9: Preparation of Declaration of Conformity (DoC)

- The manufacturer will be responsible in the preparation of the declaration of conformity to declare the intended device is made to be compliance with the directive chosen in Step 1. Lastly, placed the CE marking onto the intended device.

2.3.3 QNET LLC

QNET LLC is a United States based company that has been providing assistance to US manufacturers and small to medium sized companies with CE marking since 1996. The headquarter of QNET LLC is located in Minnesota, United States while it has a overseas authorized representative office named QNET B.V located in Amstenrade, The Netherlands (QNET LLC, 2015). The company is a consulting and training firm

that does regulatory issues and quality assurance for medical devices. QNET LLC offers both US and European manufacturers an authorized representative services for medical and *in vitro* directives.

With the operation experience of almost 22 years and more than 12 years in assisting small to medium sized companies, QNET had consolidated and formulate 7 necessary steps for manufacturers that are not from Europe to actually follow (QNET LLC, 2014) and more details are in Appendix B8.

Step 1: Determine if any directives apply to the product

- Choose the appropriate directive that is suitable for the product to be conform to.

Step 2: Determine the extent of compliance with essential requirements

- Base on the design ad manufacturing requirements in the directives, determine the extent of the product compliancy.

Step 3: Choose conformity assessment procedure from available options

- The options for the conformity assessment are available in the medical related directives and these options are based on the product risk level. Options for products with greater risks will require more testing, auditing and certification process by a notified body.

Step 4: Select applicable product standards and test methods

- The selection of the appropriate and suitable product standards will help in conforming the requirements stated in the directives. Finding of a notified body will aid the manufacturer in getting both the production and product properly tested and verified.

Step 5: Establish an authorized representative

- All the medical related directives require the overseas manufacturer to designate an authorized representative to assist in the preparation of technical documentation and also when putting the device out into the market.

Step 6: Prepare a declaration of conformity

- The declaration of conformity has to include a list of the relevant and selected directives and standards that the product is conform to. It must also include the authorized representative name and address. The DoC has to provide adequate information when tracing the product back to the manufacturer.

Step 7: Attach CE marking to the device.

- Before even attaching the CE marking on the device, the manufacturer has to adhere to these rules. The rules focus on size and location of the symbol, the CE marking has to be on product, packaging and documents that will be together with the product.

2.4 Summary

Looking back at Chapter 2 of this thesis, there is a variation in the number of decision making steps and arrangement of the companies located in the EU and United States. Figure 6 shows a summary of the steps recommended by the different companies in EU. The steps required by each companies varies from five to ten with a difference in the arrangement of the steps too.

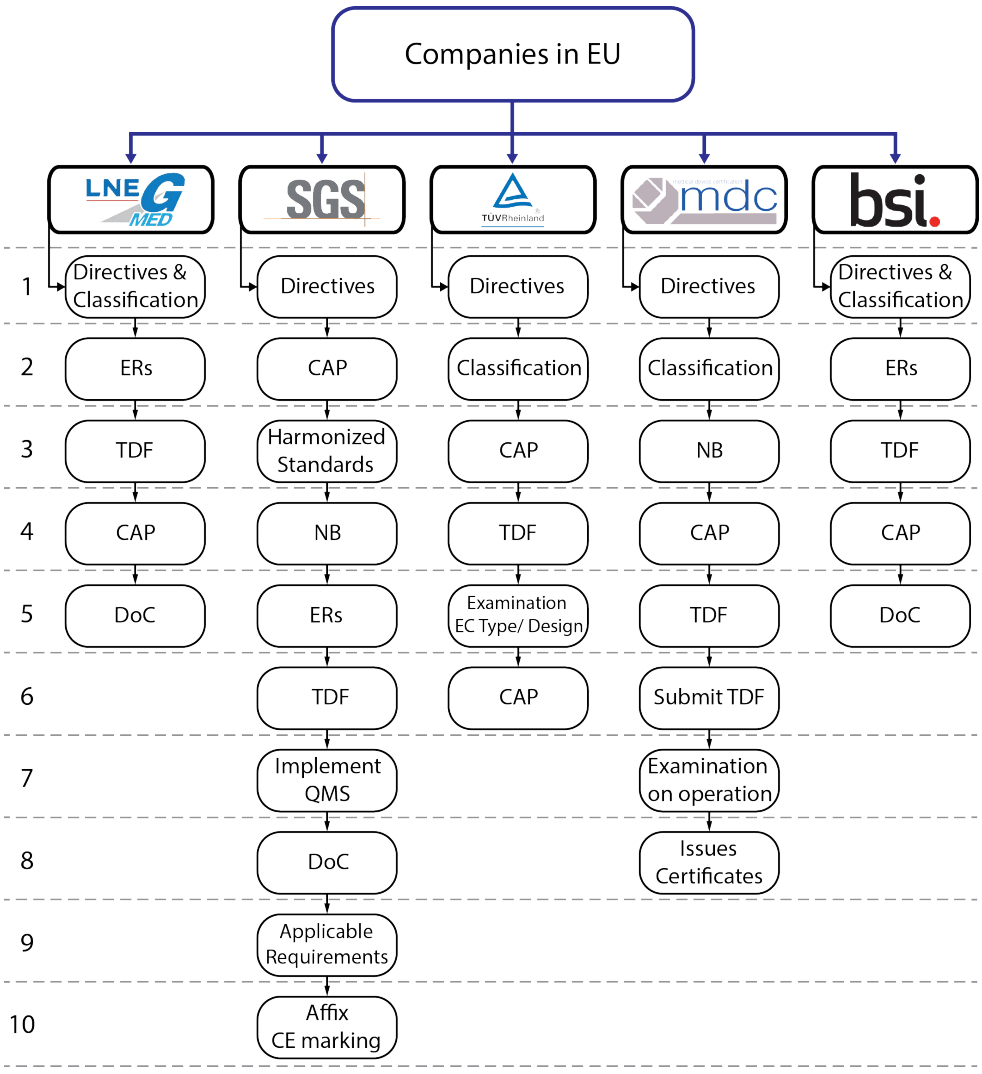


Figure 6 - Summary of Recommended Steps by Companies in EU

Figure 7 shows a summary of the steps recommended by the different companies and government body that are located outside of the EU. There might be slight variation in the arrangement but the step to be noted is the inclusion of appointing an authorized representative. These steps will later be used in the consideration of for the design of the CE medical decision model in Chapter 5.

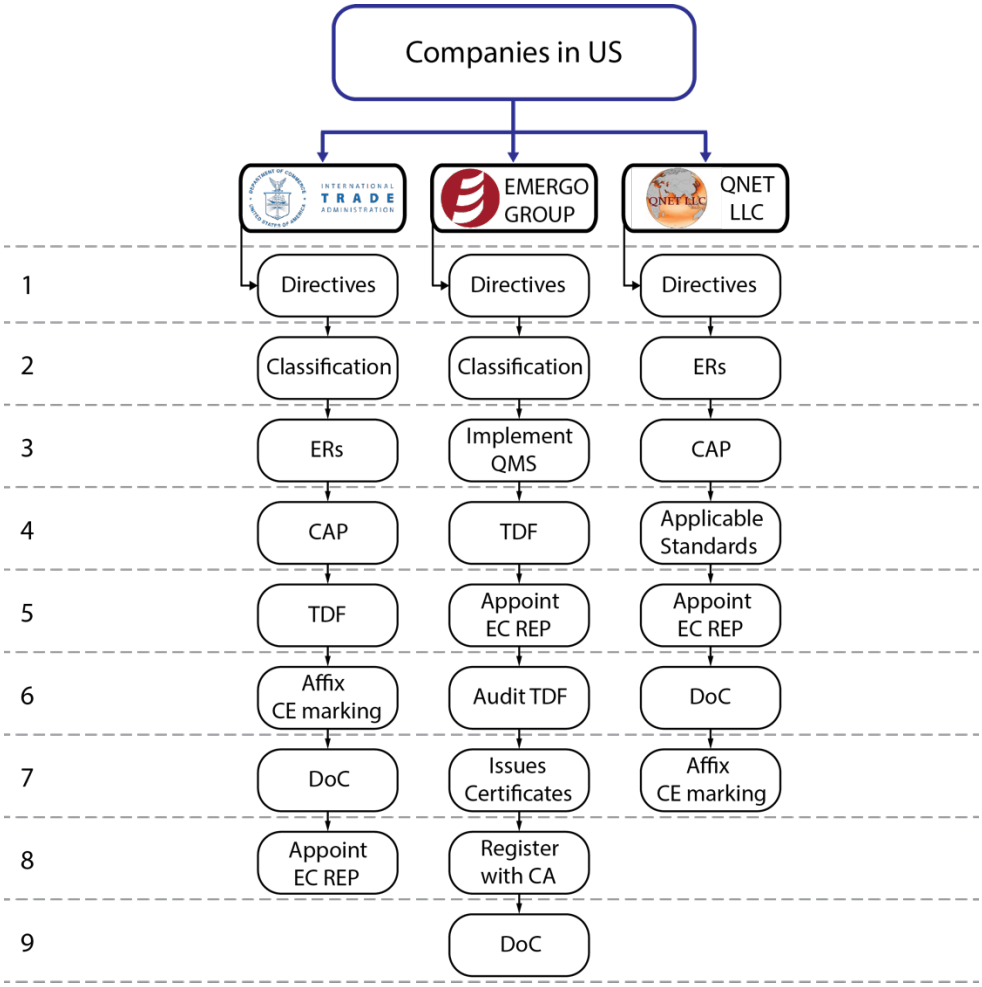


Figure 7 - Summary of Recommended Steps by Companies outside EU

CHAPTER THREE

MEDICAL RELATED DIRECTIVES AND STANDARDS

3.1 Introduction

This chapter covers an overview of the directives and standards for medical devices that are available in the EU countries. For the start, a brief explanation will be given on what does the directives for medical devices do, how many directives are there to cover the different types of medical devices and also clear definitions derived from the available directives will also be used to explain the different medical devices.

After knowing what the directives are used for and the definitions, a brief explanation on the standards will also be covered in this chapter. Standards range from worldwide level to regional to nationwide level will be briefly covered. Finally, the two most common standards (ISO 13485 and ISO 14971) that will assist in the product development will also be looked into. The ISO 13485 focus on the quality management while the ISO 14971 focus on the risk management.

3.2 Medical Related Directives

3.2.1 Overview of Medical Related Directives

The European medical device directives are the main law-making documents related to medical devices which helps to control and standardize the standards available in the quality and safety factors of the developed medical devices. The main legislation that governs the regulation of medical devices in the EU countries is the three available medical devices related directives. The three directives provide the overall outline

structure for the regulation of medical devices at the nationwide level. The three available directives in the EU are (European Commission, 2015b):

- 90/385/EEC: Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (90/385/EEC).
- 93/42/EEC: Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
- 98/79/EC: Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.

Table 2 - Available directives that focus on medical devices

Date of Enforcement	Directive Reference No.	Description	Main Focus
1990	AIMDD 90/385/EEC	Directive concerning Active Implantable Medical Devices	Active Implantable Medical Devices only
1993	MDD 93/42/EEC	Directive concerning Medical Devices	Medical Devices (Devices that are not covered in AIMDD and IVDMDD)
1998	IVDMDD 98/79/EC	Directive concerning *in vitro* Diagnostic Medical Devices	*in vitro* Diagnostic Medical Devices only

The three mentioned directives have some form of similarity in terms of the structure layout and contents available. There is also a relation between the three directives with the Active Implantable Medical Devices Directive (AIMDD) being the first version available and subsequently having the other two directives created and containing amendment of the previous directives. The relationship between the three core directives including the number of amendments and creations of other available directives are summarized in Table 3.

Table 3 - Creation and Amendment of Medical Device Directives

	Active Implantable Medical Devices	**Medical Devices**	**In vitro Diagnostic Medical Devices**
Original	Directive 90/385	Directive 93/42	Directive 98/79
Amendment 1	Directive 93/42	Directive 98/79	Regulation 1882/2003
Amendment 2	Directive 93/68	Directive 2000/70	Regulation 596/2009
Amendment 3	Regulation 1882/2003	Directive 2001/104	Commission Directive 2011/100
Amendment 4	Directive 2007/47	Regulation 1882/2003	
Amendment 5		Directive 2007/47	
Latest but one consolidated version	20.11.2003 including amendment No. 3	20.11.2003 including amendment No. 4	20.11.2003 including amendment No. 1
Latest consolidated version	11.10.2007 including amendment No. 4	11.10.2007 including amendment No. 5	11.01.2012 including amendment No. 3

3.2.2 Definitions of Different Medical Devices

The three directives comprise of information relevant to getting any properly designed, developed and with the intention of medical usage product out and placed on the EU market. Before any manufacturer who wishes to place the product on the market, he/she has to clearly understand and check if the designed product, with the intention for medical usage, does match with the definition of either a medical device, an active implantable medical device or an *in vitro* diagnostic medical device. The definition of the three different medical devices are briefly explained with relevant references to the directives.

Medical Device

Medical device, according to the definition in directive 2007/47/EC of the amendment to 93/42/EEC medical device directive, can be defined as any tool, instrument, mechanism, equipment, apparatus, software or other article; whether is it being used as an isolated device or a combination of devices which includes software designed to be used specifically in the area of diagnostic, rehabilitation and/or therapeutic purposes. The proper function of the medical device has to serve the purpose of diagnosis, prevention, monitoring, treatment, alleviation of or compensation for either a disease, an injury or handicap.

Active Implantable Medical Device

Active implantable medical device, according to the definition stated in directive 90/385, can be defined as any active (requires the means of any electrical source to operate) medical device which is designed to be fully or partly inserted, through surgical or medical means, into the human body or by medical involvement of inserting through a natural orifice (openings or hole), and with the intention to be remain inside after the procedure.

***in vitro* Diagnostic Medical Device**

In vitro diagnostic medical device, according to the definition stated in directive 98/79, can be defined as any medical device which is a reagent (a substance that is added to cause chemical reaction), reagent product, calibration tool, equipment, control material, instrument or system; whether is it being used isolated or combination, with the intention to be used in laboratory vessel for investigation of specimens; including blood and tissue donations, gotten from the human body; with the main purpose in assisting and provide information regarding the physiological or pathological state, diseases inherited during birth which causes abnormality or to observe the compatibility of the possible recipients.

3.3 Standards

Standards are generated norms or requirements which do not necessary require legal obligation. Standards are used for the purpose of uniformness through worldwide, regional or national in order to reduce the requirements variation which will lead to confusion.

The aim of standardization is to focus on the fundamental requirements in quality in order to carry out the exchanging of goods in the area of economics and technology. Standards are not specified by European Commission but by regional standards organizations and national standards bodies (NSBs). Table 2 shows the overview of the international and European standards organizations in the respective fields.

Table 4 - Overview of Regional and Worldwide Standards Organizations

Field	General	Electrotechnology	Telecommunications
Worldwide (International)	ISO	IEC	ITU
Regional (European)	CEN	CENELEC	ETSI

International Standards

International standards are worldwide standards being developed and produced by international standards organizations like International Organization for Standardization (ISO), International Electrotechnical Commission (IEC), International Telecommunication Union (ITU), American Society for Testing and Materials (ASTM) International etc. It can be used as a direct reference or may be adopted and altered by

regional standards organizations or NSBs to be applicable in the local legislation context. With an aim to overcome technical obstacles in commerce caused by the differences within regional and national standards, the usage of international standards is preferred normally unless otherwise stated.

Harmonized (European) Standards

Harmonized standards can be known as regional standards, are national standards consolidated by regional standards organizations such as European Committee for Standardization (CEN), European Committee for Electrotechnical Standardization (CENELEC), European Telecommunication Standardization Institute (ETSI), etc. or by adoption and alteration of international standards. In Europe, the consolidated national standards or altered international standards will only be recognized as harmonized standards after the announcement has been made in the Official Journal of the European Union (OJEU). Normally when referring to European standards, it is prefixed with the letters EN (European Norm) and not all European standards have undergone the process of harmonization. For European standards, it will be titled as EN {standard number]-[number of parts].

A full list of harmonized standards used for the medical devices such as active implantable medical devices (AIMD), medical devices (MD) and in vitro diagnostic medical devices (IVDD) can be found in the European Commission website.

National Standards

National standards can be known as country standards, are developed and produced by national standards bodies such as British Standards Institution (BSI) in United Kingdom, German Institute for Standardization (DIN) in Germany, National Standards Authority of Ireland (NSAI) in Ireland, Swedish Standards Institute (SIS) in Sweden, etc. With reference to any national standards, the following prefixed letters are applied as follows. For example if the reference is the use of BSI standards, it will be titled as BS [standard number]-[number of parts]:[year]. A full list of national standards bodies is included in Appendix C1.

3.3.1 Quality Management Systems for Medical Devices (ISO 13485)

ISO 13485 is an international standard on Quality Management System (QMS) for all medical devices explicitly for regulatory purposes (Goodall & Bos, 2013). ISO 13485:2003 is a standalone document and is the current international standard being used worldwide except for EU countries. EN ISO 13485:2012 is the current version of European harmonized standard and the differences are the changes within the Foreword and Annex Z which provides greater clarity on applicability & alignment with AIMDD, MDD and IVDMDD. The similarity of both standards will be that no changes made in the normative text. For this sub-section of the chapter, ISO 13485:2003 will be used to explain an overview for quality management system model. ISO 13485:2003 is mostly used in achieving the regulatory requirements when performing the registration for medical devices. A well-implemented ISO 13485 QMS will enhance the reliability and

consistency of the processes used by the company (Goodall & Bos, 2013). It will also assist in the waste and defect reduction in the production phase. In order to fully understand ISO 13485:2003, a technical report has to be used as a form of guidance and it is ISO/TR 14969 (Medical devices – Quality Management Systems – Guidance on the application of ISO 13485:2003).

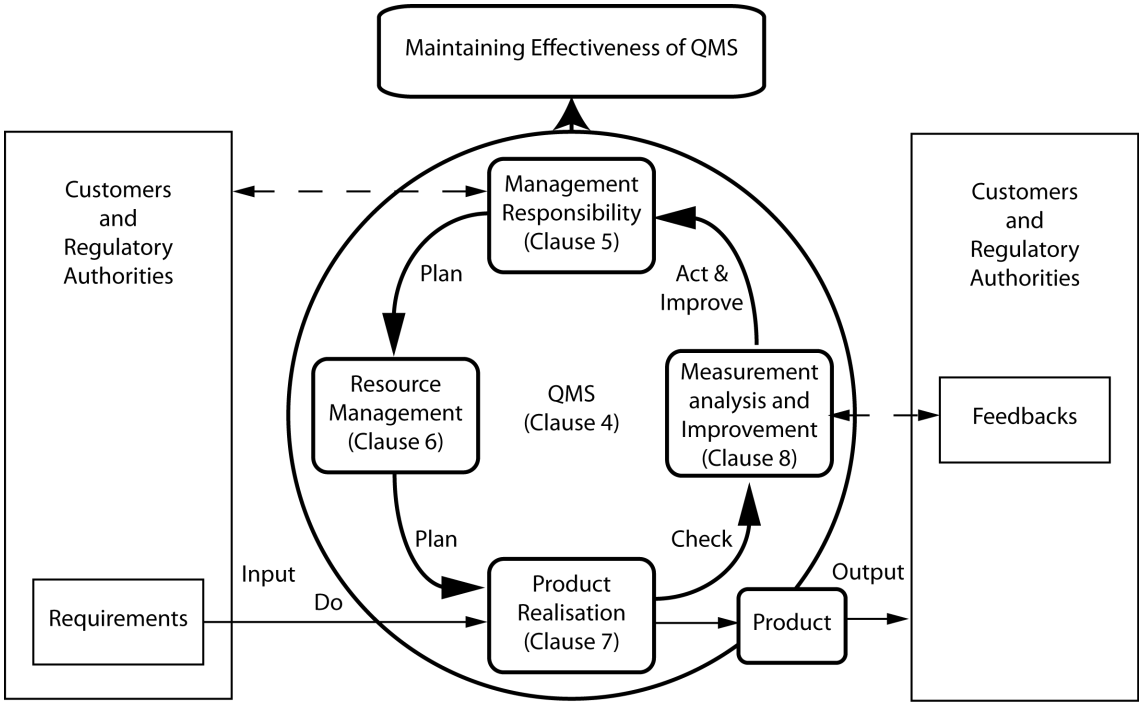


Figure 8 - Model of process-based Quality Management System

Quality System Model (Clause 4)

Quality Management System will briefly cover on two aspects: General requirements and Documentation Requirements (ISO, 2003). The general requirements will need the company to identify the processes for the QMS, determine the process sequential and relation, measures and techniques used to ensure the operation, availability of the

resources, monitoring and analysis followed by the implementation of actions to achieve planned results.

For the documentation requirements, it shall include a quality manual of the processes, control of both documents and records (ISO, 2003). Quality manual has to include the scope with details of justification, written procedures established and description of the processes. The definition of the controls needed has to be properly written in the procedure. Lastly, the records have to be properly kept and maintained so as to provide evidence of conformity to the requirements. Figure 9 shows an example of the four level quality management system used to describe the documentation requirements.

Figure 9 - Four level quality management system

Management Responsibility (Clause 5)

The management responsibility emphasizes on the responsibility of the upper management of the company. The clause focuses on the upper management commitment and obligation to the development and execution of the QMS, meeting the customer requirements, quality policy to maintain the effectiveness of the QMS, planning and management reviews (ISO, 2003). Upper management has to ensure on fulfilling the customer needs and also the quality policy which states the sole purpose of the company. Most importantly, the upper management has to plan and conduct interval reviews to uphold the required QMS standard of the company.

Resource Management (Clause 6)

The resource management will be focusing on providing the resources needed, human resource issues, infrastructure related and also the working environment of the company (ISO, 2003). The company has to properly maintain and allocate adequate resources in order to keep up the proficiency level set in the QMS. As for the human resource issues, upper management has to make sure the competency level of the workers is maintained through relevant education and proper trainings. Proper utilization of workspace, maintenance of equipment and supporting services are essential in the infrastructure section. It is very crucial to establish a good working environment for the production area as well as the workers' condition in terms of cleanliness.

Product Realization (Clause 7)

The "Product Realization" in ISO 13485 covers from the initial planning and development stages of the product to manufacturing processes required and lastly, customer service. Firstly, the company has to plan for a suitable method of operation for the product to materialize. The method of operation includes setting the quality objectives, coming out with an established procedure such as risk management activities, proper documentation, inspection on acceptability of product and finally the results on the inspection and testing.

Before the company can proceed to design and develop the product, it has to determine requirements of the product that are related to the customer process. Some of the requirements are the expectation on the product performance, design factors, delivery schedules, etc. The company must be able to establish a two-way communication for the customers to be able to feedback on the product, enquires or maybe even complaints (ISO, 2004).

For design and development phase, the various stages need to be performed: planning, inputs and outputs, review, verification, validation and the control changes. The company also has to look into the purchasing procedures, information in regards to the purchasing and the verifying of the purchased product. Finally, the production and service provision includes the control, validation of processes, identification and traceability, customer property and preservation of product (ISO, 2003).

The company has to evaluate the purchasing procedures and purchasing information with the suppliers and perform a verification of the purchased product. The production

line has to be carried out under a controlled condition such as cleanliness and contamination control. The servicing of products should be included as warranty coverage or stated in the contract (ISO, 2004).

Measurement Analysis and Improvement (Clause 8)

Clause 8 emphasize on the monitoring and measurement of the product, the control of non-conforming product, evaluation of data and improvements. Monitoring and measurement includes feedback from customers on the product and internal auditing on interval basis (ISO, 2003). Products that do not conform to the requirements have to be restrained from delivery or misused purpose. The company will then analyze the data collected to further decide on the possibility of improvement in the effectiveness of the QMS. Lastly, the improvements can be performed through corrective action or preventive action. The corrective active is used to stop any reoccurrence in a nonconforming situation whereas preventive action is to prevent the nonconforming situation from happening at any moment.

3.3.2 Application of Risk Management to Medical Devices (ISO 14971)

The ISO 14971 is an international risk management standard for all medical devices and is designed to be compatible with ISO 13845. ISO 14971:2007 is the current standard used in other countries except in EU countries and is a replacement of the year 2000 edition (ISO 14971:2000) (Chan & Tong, 2013). The EN ISO 14971:2012 is the current European harmonized standard and is the third edition to EN ISO 14971:2007

which is an adopted ISO standard by European standard previously. The similarity between the international standard and the European version is that the clauses or requirements stated in both standards remain exactly the same but the difference is that there is a slight change within the Foreword and Annex Zs of EN ISO 14971:2012. This part of the chapter will only be focusing on the clauses of ISO 14971:2007 which is exactly the same as EN ISO 14971:2012 (Chan & Tong, 2013).

The framework of ISO 14971:2007 consists of the following elements: Risk Management Policy, Risk Management Plan, Risk Management Process and Risk Management File (Chan & Tong, 2013). Figure 10 shows the full lifecycle of ISO 14971:2007 model with an outline of each element.

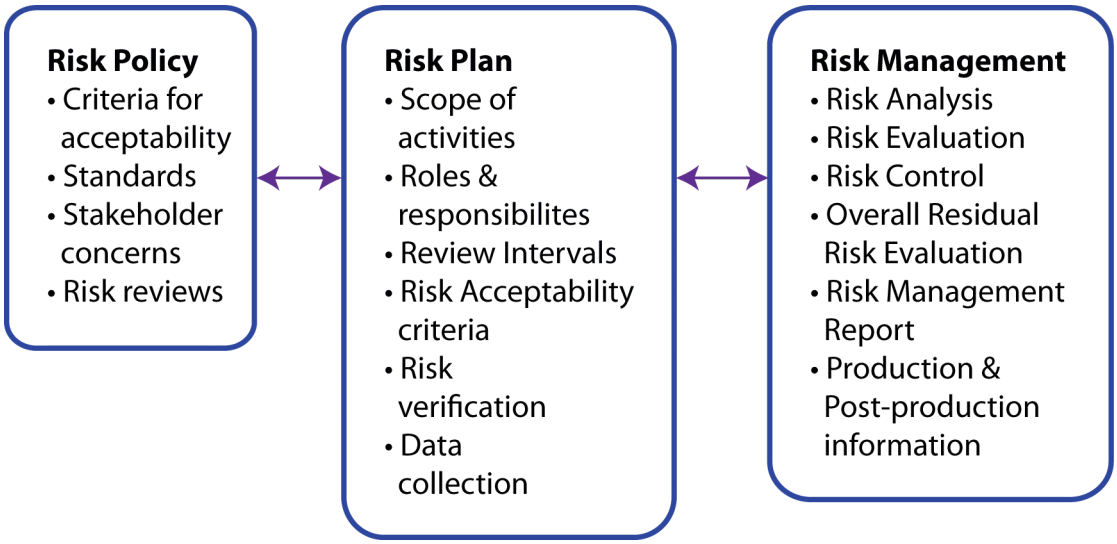


Figure 10 - Full lifecycle of ISO 14971:2007 model

Risk Management Policy

The management of a company should document the RM policy by taking into consideration of the appropriate and related worldwide, nationwide, regional or harmonized standards and regulation (Chan & Tong, 2013). The RM policy should include an explanation on determination of the risk acceptability and also a periodic review of the risk management activities. Most importantly, the RM policy should be in place before the commencement of the RM process.

Risk Management Plan

Every product that the company develops should be prepared with a well-established RM plan. The RM plan can be further developed into templates for the use on other similar products (Chan & Tong, 2013). The RM plan mainly refers to the risk acceptability criteria that are defined in the RM policy as shown in Figure 10. The RM plan outlines the RM process needed and must include the following elements:

- Scope of RM activities (including life cycle)
- Roles and responsibilities
- Intervals for review of RM
- Risk acceptability criteria
- Verification of the available risks
- Performing data collection during and after the production activities

Risk Management Process

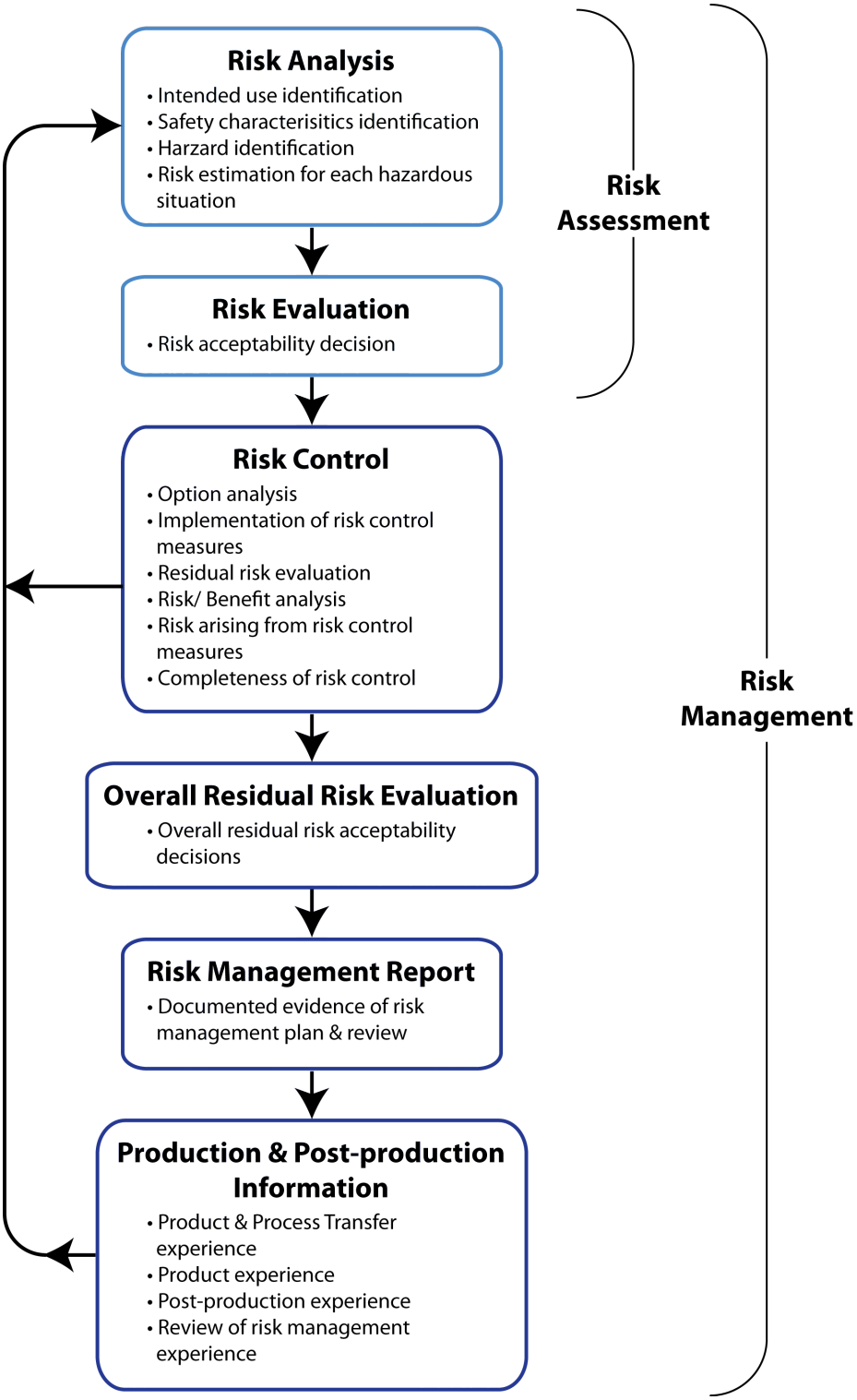


Figure 11 - Risk Management Framework

Risk Analysis (Clause 4)

The risk analysis requires the company to familiarize with the product; understand the intended purpose and anticipatable abuse or mishandling of the developed product; detect recognizable and probable dangers and estimate the necessary risk level for each dangerous or harm threatening condition (ISO, 2007). It is a must to familiarize thoroughly the requirements in the development of the product before the commencement of any RM activities. With a good understanding in the intended purpose of the developed product, this will form a basis in identifying any known and/or foreseeable dangers beforehand. Once the hazards have been clearly identified during the risk analysis stage, the severity and chances of occurrence in the harm level is required to be assessed and subsequently generating a score in the risk level of the identified hazard (Chan & Tong, 2013).

Risk Evaluation (Clause 5)

Each hazardous situation has to be assessed against the risk evaluation criteria properly outlined in the RM plan. In general, there are three kinds of action needed to be performed in the risk acceptability decision which will depend on the level of risk defined in the criteria (ISO, 2007). Firstly, the risk can be accepted without additional actions to be taken if the risk level is low. Secondly with a risk level that is extremely high, control measures are required to be implemented immediately in order to decrease the risk level to a tolerable level. Last but not least, the risk level that falls on the marginal line is required to be further investigated with a risk/benefit analysis before any decision can be made.

Risk Control (Clause 6)

The two main components that the risk controls will be looking at are the possibility of occurring in harm factor and the severe condition level in harm factor. Generally, the possibility of occurring in harm factor will be a lot easier to maintain or even minimized as compared to the severe condition level in harm factor. The risk control measures should consider the following (ISO, 2007):

- Design with essential safety being considered (most preferred choice)
- Products or production with protective measures in place
- Information for safety (least preferred choice)

Overall Residual Risk Evaluation (Clause 7)

The overall evaluation on the residual risk is to evaluate the acceptability of overall residual risk in a developed product (ISO, 2007). The risk acceptability criteria are being defined in the RM plan. With the risk control measures properly carried out and documented, the overall residual risk will then be reviewed. The evaluation of the overall residual risk will then be used to determine the level of effectiveness in the applied risk control measures. If the evaluation of the overall residual risk is deemed to be intolerable, a decision has to be considered if the medical benefits prevail over the risk itself.

Risk Management Report (Clause 8)

During the pre-release of the product, the company must summarize and perform an assessment on Step 1 to Step 4 as a RM report. A review is necessary so as to ensure the RM plan is properly carried out; the overall remaining risk is in the tolerable range or level and appropriate measures are executed in obtaining the information during and post production. Thus, the review outcomes will then be consolidated and filed as the RM report and it is included in the RM file.

Production & Post-production Information (Clause 9)

The emphasis on this clause is the information gathered after all the risk measures/controls in Step 3 has been carried out (Chan & Tong, 2013). The company should have a systematic process in retrieving information about the device during and after the production phase. The collected information for the production phase should include the design to production, certified procedures and the controls, etc (ISO, 2007). For the post-production phase, the information gathered must include the product installation and servicing reports, complaints or feedbacks by customers, possibly latest or amended standards and finally the information on possible alike products. Once the collected information has been evaluated, the results should be used as an aid in the RM process in Step 1 ad having the RM process start over again with the new possible risks to be analyzed.

Risk Management File

The RM file can be stored as either electronic records or hardcopy records. The records of the identified hazards are found in the results gathered from Clause 4 to Clause 7 of the RM Process. These records have to be traceable and stored in the RM file. Apart from the records of identified hazards, the RM policy, RM plan, RM report and post-production information should also be included as well. It is very crucial that the RM file is properly stored and easily accessible as it provides the essential proof or both the regulatory compliance of the product and the lawful purposes (ISO, 2007).

3.4 Summary

In this chapter, it is clear that three directives are being used to govern all the available medical devices in Europe. With a wide spread of medical devices, the initial directive that only governs active implantable medical device further developed two more directives that can govern the general medical devices and specifically the *in vitro* diagnostic medical devices. Definitions are clearly defined for the manufacturers in the sole purpose of segregating the different medical devices that are available and as such only one of the medical device directives can be applied to the intended product.

Furthermore, the definition of the different kinds of standards available are also being explained. The standards work hand in hand with the selected directive to help the manufacturers. Both the ISO 13485 and the ISO 14971 are international standards that can help in both the company and product development as it focuses on the quality and

risk management. In the later chapter, the directives will be used as one of the decision consideration in the designing of CE medical decision model.

CHAPTER FOUR

FORMATION OF CE MEDICAL DECISION MODEL

4.1 Introduction

The aim of this chapter is to design a decision model for researchers and developers to include the considerations needed to fulfill the regulatory requirements before any commercialization can take place. The CE Medical decision model aims to help researchers by providing the knowledge on the requirements in order to obtain the CE marking on the developed product that is applicable to the AIMD, MD or IVDMD directives.

Before the designing of the CE medical decision model, the building blocks of the CE medical decision model will be introduced. These building blocks are the classification or categorization of the products, the conformity options available in the directives, the requirements listed, the analysis done need to be done for the risk, the necessary documents for submission and lastly a showing of conformity with the declaration document.

The design of the CE medical decision model consists of six major steps required to be performed during the research development work before the researcher is able to have the product ready to benefit the healthcare consumers. These CE medical decision model is a combination of the building blocks elaborated in the later section and with references for the companies elaborated steps in Chapter 2.

4.2 Building Blocks for CE Medical Decision Model

4.2.1 Classification/ Categorization of Medical Devices

Active Implantable Medical Devices (AIMDs)

In accordance to the definition of AIMDs in AIMDD, the AIMDs are naturally being classified as an elevated or high risk level devices with the crucial identifiers of the devices being active and also invasive. Any devices that are being covered under the AIMDD, must not and cannot be covered under other medical related directives like MDD or IVDMDD. Some examples of the devices that can be under the AIMDDs are implantable defibrillator, implantable pacemaker, active implantable drug administration devices, etc.

Medical Devices (MDs)

In accordance to the definition of MDs in MDD, the MDs are being classified within a range from low risk to high risk level devices. In terms of practicality and economically, the medical devices are classified in a tiered approach that will be appropriate according to the regulatory requirements. Figure 12 shows the relationship of how the medical devices can be classified with reference to the MDD.

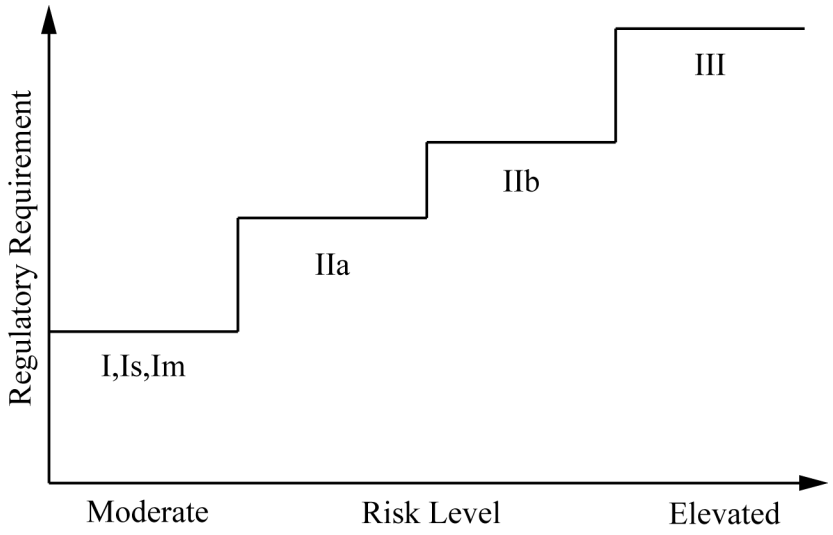


Figure 12 - Relationship between risk level and regulatory requirements in MDD

The medical devices are split up in four different classes based according to their risk level: Class I (moderate/ low risk), Class IIa and IIb (average/ medium risk) and Class III (elevated/ high risk). In order for manufacturers to make a decision on which class should the manufactured device to be classified in, there are criteria and rules specified and elaborated in Annex IX of MDD to provide assistance. The criteria that are listed in Annex IX of MDD focus on these areas with definitions: length of time for contact (for uninterrupted usage of: (transient) less than an hour, (short) thirty days or less, (long) thirty-one days or more), level of invasive (penetrates the body through natural opening in the body or with the aid of surgical operation), mode of action (either does the device requires the dependency on a source of electrical energy or not), implantable (introduced to the body and stays in place after operation means) and specific hazards. After the list of criteria with definitions, there are eighteen rules set up for implementation with the aim to assist the classification procedure of the manufactured

device: four paths focus on non-invasive devices (Rule 1 to 4) in Figure 13, four paths focus on invasive devices (Rule 5 to 8) in Figure 14, four paths focus on active devices (Rule 9 to 12) in Figure 15 and lastly six paths focus on devices with special rules to be applied (Rule 13 to 18) in Figure 16. Table 5 shows a few examples for the different classes of MDs based on risk level.

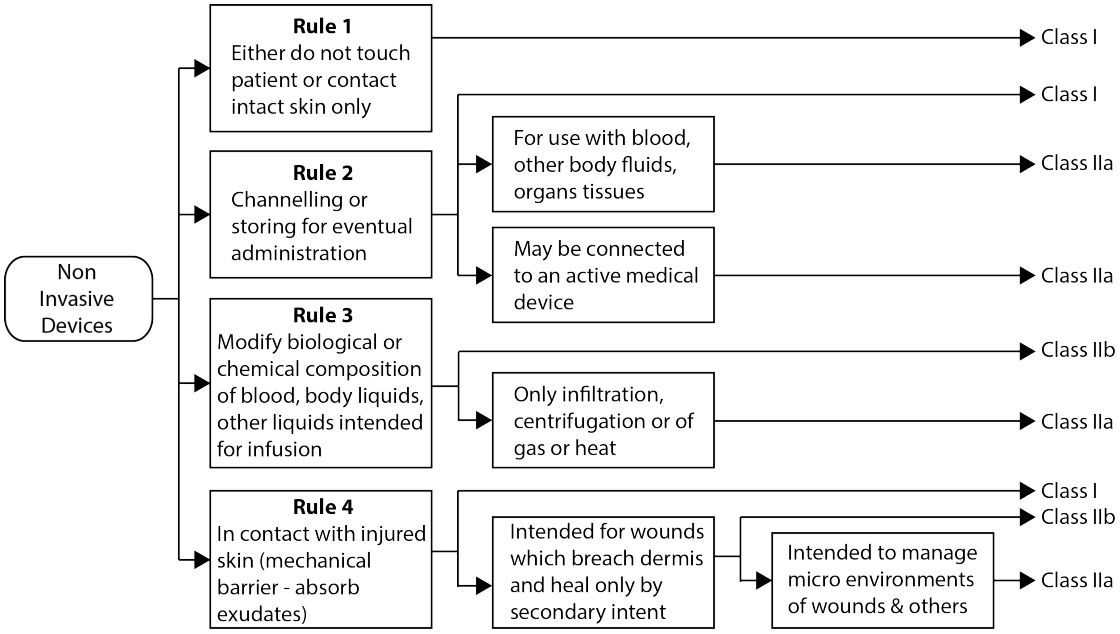


Figure 13 - MDD rules (1 to 4) for classification of Non Invasive Medical Devices

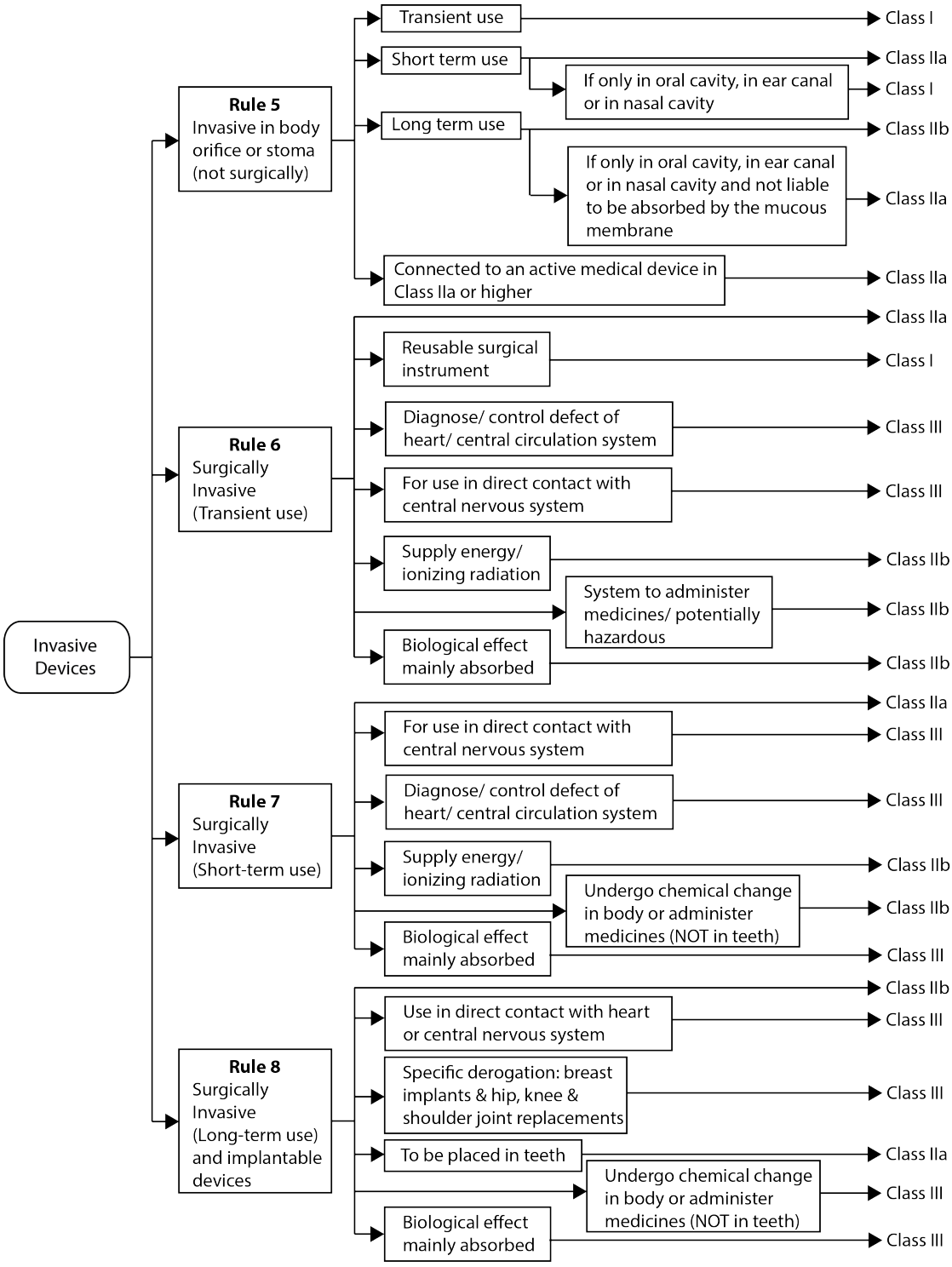


Figure 14 - MDD rules (5 to 8) for classification of Invasive Medical Devices

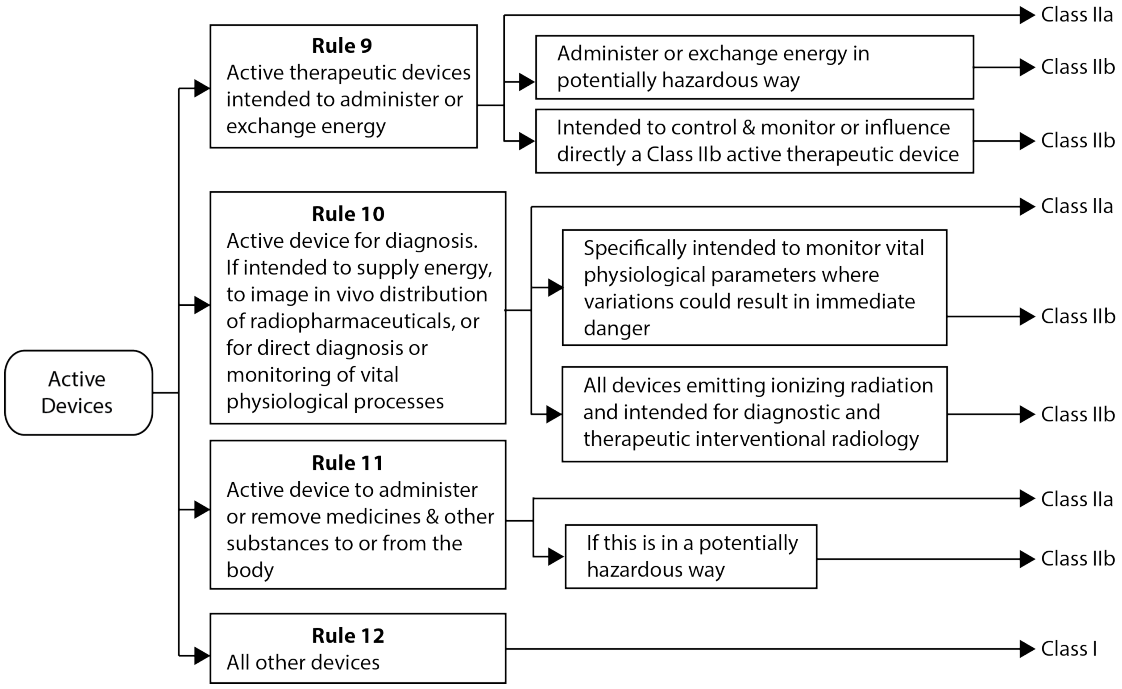


Figure 15 - MDD rules (9 to 12) for classification of Active Devices

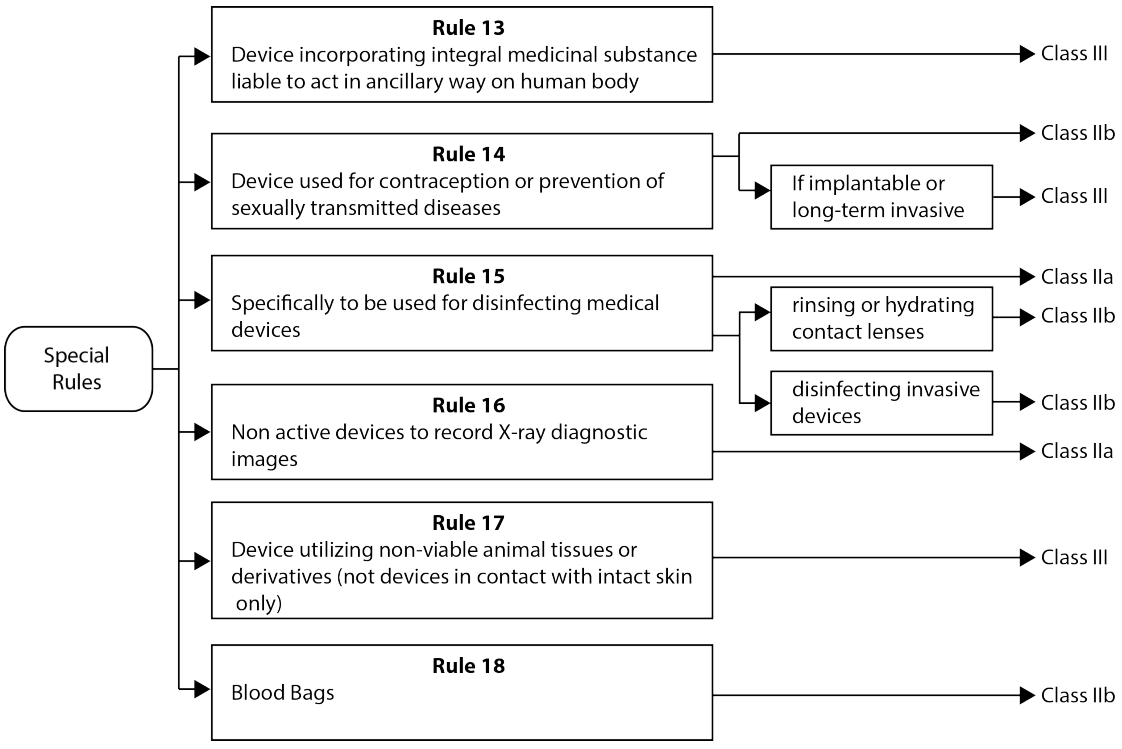


Figure 16 - MDD rules (13 to 18) for classification of Devices with special rules

Table 5 - Medical device examples based according to classification

Classification	Risk Level	Medical Devices under Class
Class I	Moderate/ low	Hospital beds, examination gloves
Class Is	Moderate/ low (sterile)	Sterile alcohol swabs
Class Im	Moderate/ low (with measuring function)	Body temperature measuring device, syringe without needle
Class IIa	Average (Moderate)	Attached needle with syringe, contact lenses for short duration
Class IIb	Average (Elevated)	Insulin pens, contact lenses for long duration
Class III	Elevated	Spinal needle, neurological catheters

in vitro Diagnostic Medical Devices (IVDMDs)

In accordance to the definition of IVDMDs stated in IVDMDD, the IVDMDs are being categorized and not classified like MDs. The IVDMDs are categorized in an order based on their risk level of usage and split up in four different categories with reference to Annex II in IVDMDD. Figure 17 shows the relationship of the amount of regulatory requirements required based on the risk level of the IVDMDs in order to be categorized.

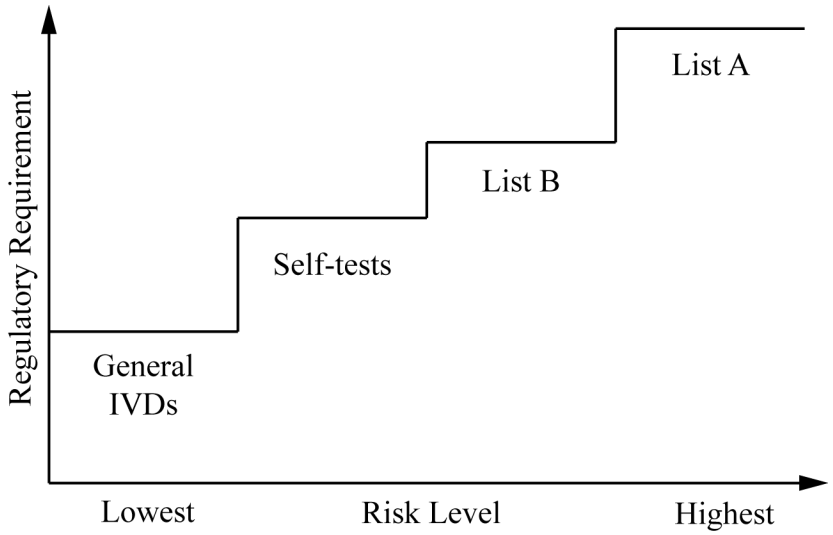


Figure 17 - Relationship between risk level and regulatory requirements in IVDMDD

The *in vitro* devices are being categorized according to four categories: List A IVDs, List B IVDs, IVDs meant to be self-testing and all other general IVDMDs. Table 6 shows a few examples where the different categories of IVDMDs are being used for.

Table 6 - IVDMDs examples based according to categorization

Categorization	Risk Level	IVDMDs under Category to determine
General IVDMDs	Lowest	Tests for hormones, cardiac markers, hematology and clinical chemistry tests
Self-test IVDMDs	Interim	Pregnancy tests, cholesterol home tests
List B IVDMDs	Interim	Rubella (inborn infection), tissue groups, PSA (tumoral marker), blood glucose for self test
List A IVDMDs	Highest	Hepatitis, ABO blood grouping, HIV infections

4.2.2 Conformity Assessment Options

After a manufactured device has been classified or categorized by the manufacturer, the CE marking procedure must be followed depending on the classification or categorization of the device. The conformity assessment options come under the CE marking procedure and there are multiple options available to select and is dependent according to the class or category device with the accompanying risk level. The strictness level of the conformity assessment options is much higher for high risk level devices when comparing to low risk level devices. The overview of the relevant annexes for all three medical related directives is shown in Table 7.

Table 7 - Annexes available in three medical related directives

Name of Annex	Annex in AIMDD	Annex in MDD	Annex in IVDMDD
Full Quality Assurance	2	II	IV
Type Examination	3	III	V
Verification	4	IV	VI
Quality Assurance on Production	5	V	VII
Quality Assurance on Product	Not available	VI	Not available
EC (Self) Declaration of Conformity	Not available	VII	III

The manufacturer has to follow according to the chosen conformity assessment options in order to move one step closer to getting certified by a notified body in the CE marking and subsequently placing the CE marking symbol on the device and its related

documents. The main aim of having the conformity assessment options available in the directives is to make sure any manufactured devices is being designed while fabricated with compliance to the requirements stated in Annex I/ 1. The manufactured device is subjected to conformity assessment which covers both design and production phase. There are a total of eight modules named with the letters from A to H (Tan, Heng, Chua, & Foo, 2015). Figure 18 shows the overview of the assessment route of the modules which is needed during design and production phase. The conformity assessment options do require the involvement of the notified body for most cases but with the exception of low risk level medical devices. These devices only require the manufacturers to do a self assessment and draw up a self declaration conformity document according to Annex VII (MDD) or III (IVDMDD). In Table 8 shows the certification activities available while performing the relevant conformity assessment options on the device.

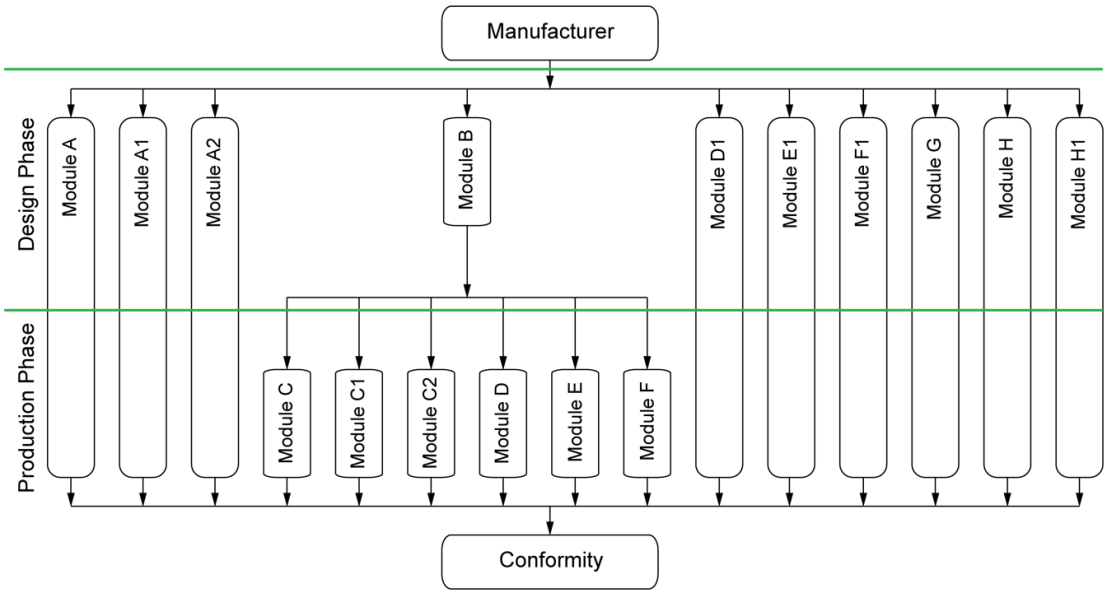


Figure 18 - Overview of the conformity assessment modules (A to H)

Table 8 - Certification activities in relation to conformity assessment options

Certifications for quality in systems	Full QA System Certification	Audit against the standard for the quality check of designs, manufacturing procedure and final review
	Production QA System Certification	Audit against the standard for the quality check of manufacturing procedure and final review
	Product QA System Certification	Audit against the standard for the quality check of final review
Certifications for device related	Design Inspection Certification	Inspection of the design dossier in accordance to directive requirements and associated standards
	Type Assessment Certification	Analyzing and testing of a device sample in accordance to directive requirements and associated standards
	Verification Certification	Analyzing and testing of entire batch samples in accordance to directive requirements and associated standards

The conformity assessment options can be performed following a single module or coupled with other modules as shown in Figure 18. In Figure 19 shows the conformity

assessment options in term of annexes in directives for either the classification or categorization of the devices.

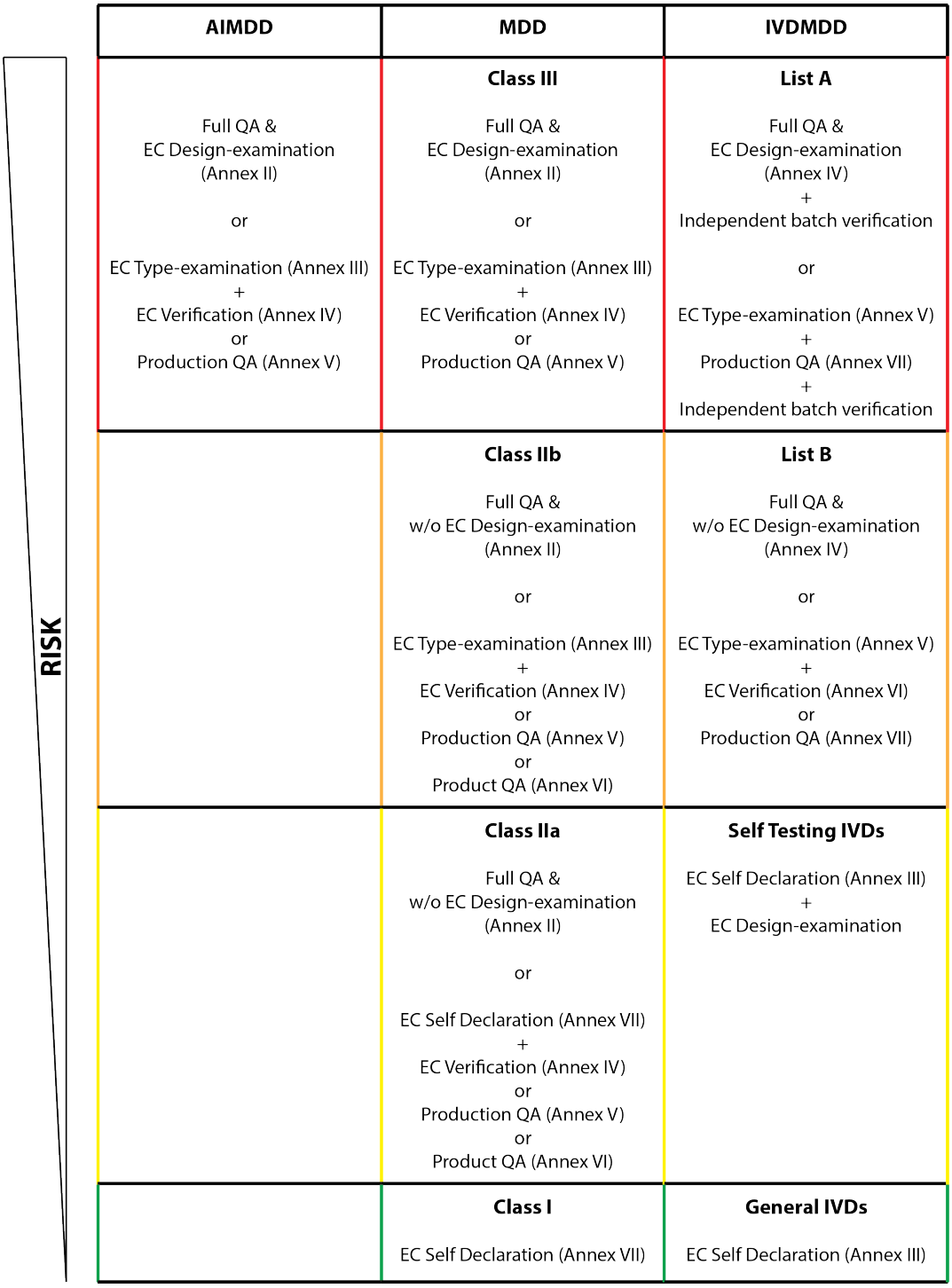


Figure 19 - Conformity assessment options for manufacturers on different medical devices

Full Quality Assurance

The most high-priced but effective option/ route for all high and medium risk level medical devices is to perform a full check on the quality assurance in Annex II (AIMDD & MDD) or IV (IVDMDD). The main responsibility of the manufacturer is to maintain a good management in the quality system in accordance to ISO 13485 on the designing phase, manufacturing phase and the final review of the manufactured product. The manufacturer has to do up an application and make a submission to the selected notified body with necessary details of the manufactured device including documents describing on the quality system (Tobin & Walsh, 2008). The notified body will then proceed to have the system being inspected for quality while the technical documents or design dossier reviewed. The main difference in the procedure for the high risk and medium risk medical devices is the design examination can be excluded during the inspection for quality assurance. After having the quality and design inspection performed, the notified body will then confirm the quality system and proceed with issuing a certification for the design inspection on the manufactured device (Tobin & Walsh, 2008). The notified body will perform a random audit check on the quality system every now and so in order to make sure that the manufacturer does adhere to the compliance of the design inspection certification.

EC Type Examination

This route of conformity assessment is chosen when the manufacturer wants to have the manufactured device representative to be certified by the notified body. For this chosen route, there is no inspection on the quality system. The manufacturer has to do

up an application and make a submission to the notified body with details on the design of the device and representative sample of the production (Tobin & Walsh, 2008). The notified body will then proceed with the reviewing and assessing of the documentation details and perform appropriate inspections and tests on the representative sample. Once the representative sample conforms with the requirements in the related directive, the certification of EC type examination will be issued by the selected notified body to the manufacturer (Tobin & Walsh, 2008).

EC Verification

This route of conformity assessment is chosen when the manufacturer wants to go through EC verification other than the quality assurance on the production. This route requires the testing of all or a selective sampling of devices for each batches and will be done by the notified body. After the completion of testing on the batches, the batches can then be placed on the market after a certificate has been written with the tests done. If any batch is deemed not acceptable, that particular batch cannot be placed on the market. Apparently this route is not a favorable choice for manufacturer because of the high cost needed to do verification and it does not provide sufficient assurance in term of the sterility of the devices (Tobin & Walsh, 2008).

Quality Assurance on Production

This route of conformity assessment is chosen when the manufacturer wants to implement a system of quality in the manufacturing process and have it checked and proved by the notified body. For this route, the ISO 13485 can be used to help the

manufacturer in achieving compliance in the quality for the manufacturing process. This route does not include the application of quality system on the design and development portion. The manufacturer is required to do a submission of an application on the quality system of the manufacturing process to the notified body. The application must contain evidence on any appropriate EC type-examined device and the documentation containing the quality system in the manufacturing process (Tobin & Walsh, 2008). The notified body will then perform an audit on the quality system and do an inspection on the premises. The notified body may perform a random audit check on the quality system of the premises every now and then in order to make sure that the manufacturer does adhere to the compliance.

Quality Assurance on Product

This route of conformity assessment is chosen when the manufacturer wants to implement a system of quality in the final review and testing of the product and have it approved by the notified body (Tobin & Walsh, 2008). This route focuses on the final review and testing of the product so as to make sure the product produced is an approved type. The manufacturer is required to submit an application to the notified body for the auditing of the final inspection and testing of the product only. The notified body may perform a random audit check on the quality system of an adequate samples of the final products every now and then in order to make sure that the manufacturer does adhere to the compliance.

Self Declaration of Conformity

For this route of the conformity assessment, manufacturers do not need to involve any notified body but is required to perform a self assessment on the manufactured device before making a declaration of conformity for the device. But there is a particular case for the medical device when it has a measuring function or requires to be sterile, a notified body is needed to assure that the sterilization process is properly done (Tobin & Walsh, 2008).

4.2.3 Essential Requirements

All the three medical related directives (AIMDD, MDD and IVDMDD) contain a particular information on the essential requirements stated in Annex I/ 1 under the respective directives. The annex provides a general description about a list of necessary safety requirements for any medical related devices and it is a must to comply with these stated requirements before obtaining the CE marking.

The essential requirements are being divided into two main focuses: the general requirements and requirements concerning on the design and production which includes the safety and performance aspects (Teysseyre, 2013). In the general requirements section, it focuses on the generic issues like the characteristics and performances that requires consideration when designing and manufacturing the device. In the section of designing and fabricating, it focuses on a more in depth issues that the manufacturer might faced. The issues that requires to look into are: the properties related to chemical or biological, contamination related, properties related to

environmental, function for measurement, radiation protection and powered or connected to an energy source (Teysseyre, 2013). A reliable method to actually fulfilled the requirements listed out in Annex I/ 1 is the used of the European harmonized standards. This method provides practical ways for the manufacturer to comply with the requirements stated in the respective directives.

4.2.4 Risk Analysis

The analyzing of the risk for the manufactured device is normally implemented in order to make sure on the health and safety protection for the consumer are in placed. The ISO 14971 is a standard which can assist the manufacturer by providing guidance in relation to the management of the risk level. The manufacturer is required to construct and maintain a risk procedure that involves analyzing of risk, evaluating of risk, controlling of risk level, during manufacturing and after manufacturing information. The details of the whole risk procedure can be found in Chapter 3.

4.2.5 Technical Documentation File/ Design Dossier

Technical file is a documentation record of the device being compliance with the essential requirements. Design dossier is a documentation record which requires both the compliance with essential requirements and a design examination of he device. The technical documentation content is highlighted and briefly described in each annexes of the respective directives in relation to the conformity assessment route. Based on the designated class or category that the medical device falls under, an involvement of the notified body is necessary to perform a review and inspection of the quality or technical documentation (NB-MED, 2010). The technical documentation written by the NB-MED serves to provide guidance to the manufacturers in the preparation of the relevant details needed in the documentation files. As it is a guidance document written by NB-MED, the contents needed by some notified bodies may have a slight variation. Table 9 shows a summary of the contents needed for both the technical file and design dossier. The manufacturer is required to keep the technical documentation of the related devices for at least five years and must maintain the availability of it when checked by the notified body or authorities.

Table 9 - Summary of contents for technical document and design dossier

Contents	Documentation	
	Technical Document (Low - Moderate Risk)	Design Dossier (High Risk)
Regulatory information	Partial	✓
Product description/ Intended use	✓	✓
Components/ Materials/ Packaging composition	✓	✓
Design verification and results	Nil	✓
Product Realization including drawings of design and manufacturing, etc.	Partial	✓
Sterilization	✓	✓
Stability data	✓	✓
Risk management	✓	✓
Biocompatibility	✓	✓
Clinical evaluation	✓	✓
Post-market surveillance	✓	✓
Labelling	✓	✓
Checklist for essential requirements	✓	✓
List of applicable standards	✓	✓

4.2.6 Declaration of Conformity

The conformity declaration document is a compulsory legal record for the CE marking procedure as it requires the manufacturer to make sure and declare that the manufactured device does indeed fulfill the applicable requirements of the respective

directives (Teysseyre, 2013). This conformity document requires some key components to be documented before the signatory of the manufacturer. The document has to include the most important information of the manufacturer such as the company name and place of business, the authorized representative particulars; the device details like name, type and/ or model; device class or category according to applicable directive; standards applied for proving of compliance; chosen conformity assessment route; notified body particulars including the identification number; place and date of issue; and lastly a signature of the manufacturer (Haggar, 2003).

4.2.7 Affixing the CE Marking

The location of the symbol/ marking must be placed on the device, packaging and instruction for use or manual. Before the placement of the symbol, some rules have to be adhere accordingly like the CE marking must be at least 5 mm in height or if the symbol size has to decrease or increase for some particular reason, it has to fulfill the proportional size of the marking. The only allowable condition for the CE marking not to be placed on the device is when the allocated space is too limited to fit in the minimum height of 5 mm. Figure 20 shows the required size and dimensions of the CE marking.

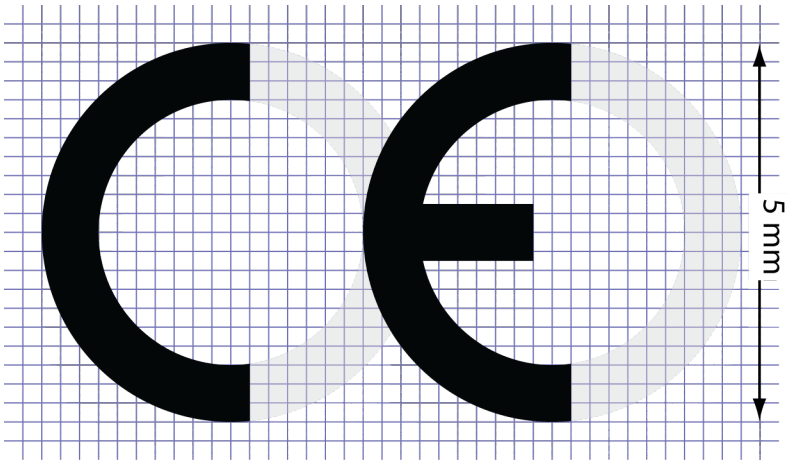


Figure 20 - Dimensions for CE marking of Conformity

In most of the cases for medical devices, the CE marking is required to include the identifying number which will indicates the selected NB with an exception in the devices of Class I only that does not require sterilization or have a function for measurement. In the cases for IVD medical devices, it is mostly similar to the medical devices where only the self declaration category does not require the notified body number to be attached. Figure 21 shows the inclusion and exclusion of the NB identification number together with the symbol.

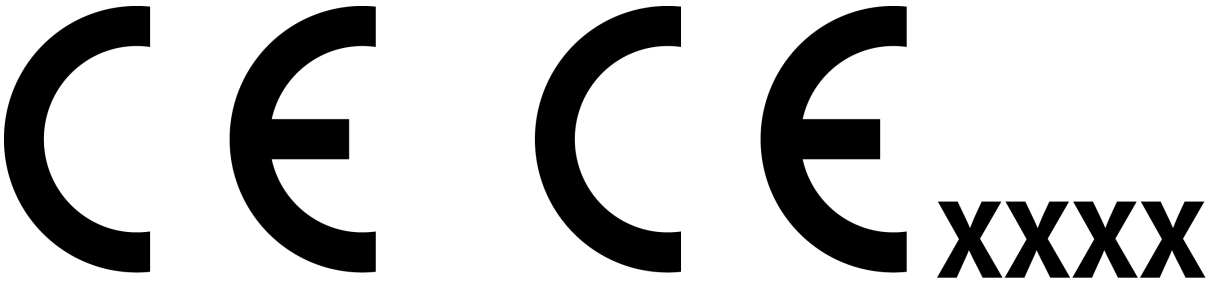


Figure 21 - Inclusion and exclusion of NB identification number

4.3 Designing of CE Medical Decision Model

The CE medical decision model is designed to assist researchers in guidance of he regulatory issues that needed to be addressed while during the development of the intended medical product. The CE medical decision model provides decisional steps that will allow researcher to make simple decision with minimal references needed. The CE medical decision model comprises of six major steps, which is a combination of the building blocks in the previous section and the steps recommended by the various companies of EU and US, that will assist in getting a CE marking for the developed product.

These six important steps are there to guide the researcher in the decision making process on deciding how to getting the developed product out in to the market. Figure 22 shows the overview of the six stages or steps in the CE medical decision model and they are also listed out accordingly:

- Step 1: Identify applicable medical related directive(s) by definition & exclusion written in Article 1
- Step 2: Verify product essential requirements in Annex 1/ I
- Step 3: Requires the involvement of notified body due to class/ category
- Step 4: Selection of conformity assessment route and declaration of conformity
- Step 5: Do up and maintain the availability of technical documents
- Step 6: Attached and placement of CE marking

The steps in the CE medical decision model will be abundantly elaborated with the inclusion of sub-steps to provide the researcher not only the overview but with the application of the building blocks from the previous section of Chapter 4.

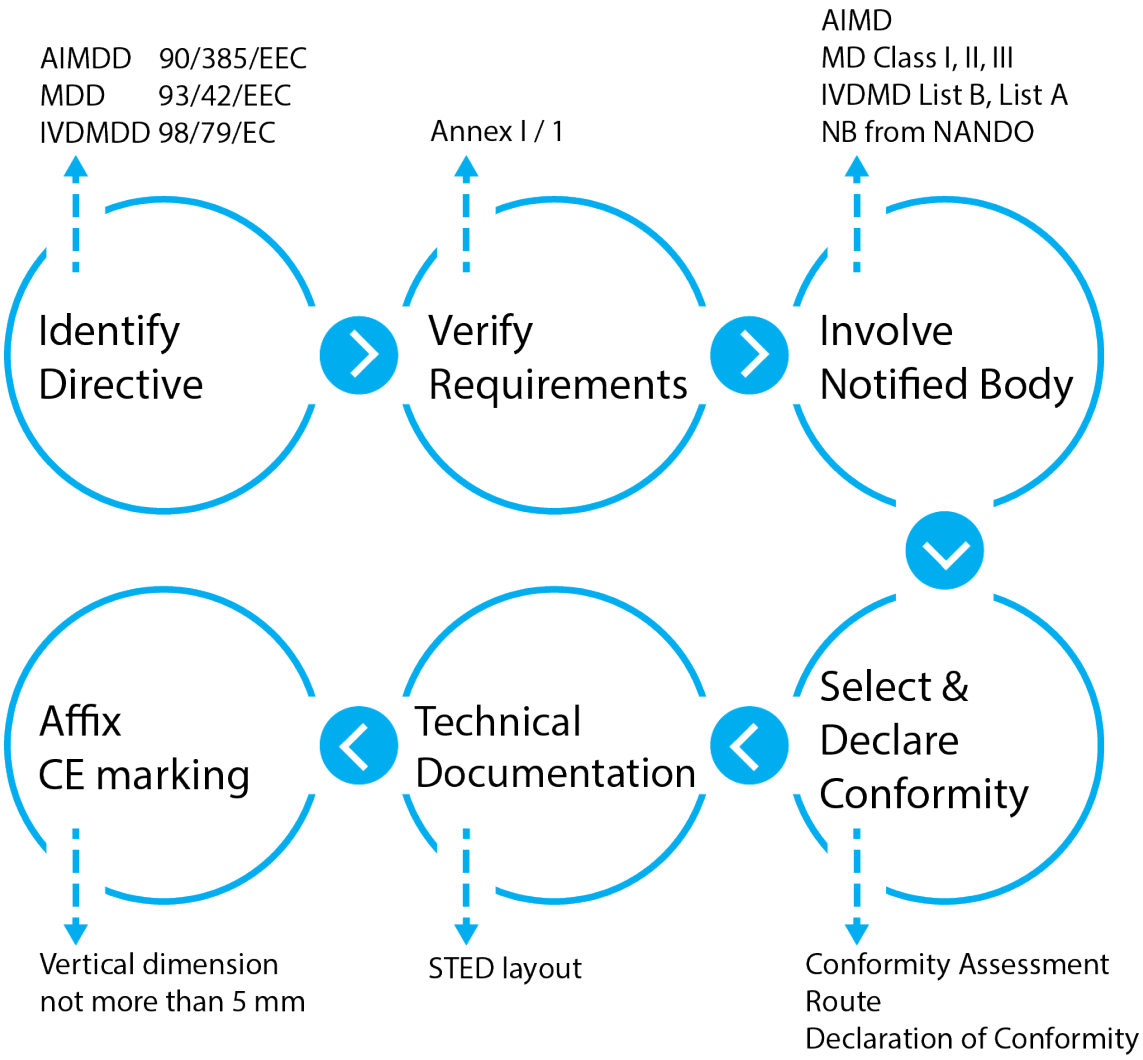


Figure 22 - Overview of CE Medical Decision Model

Step 1: Identify applicable medical related directive(s) by definition & exclusion written in Article 1 ('Identify Directive' in Figure 22)

a) Find out whether the intended device fulfills the definition of either one of the medical related directives
    - AIMDs: Definition can be found in Article 1, paragraph 2a (medical device), 2b (active medical device), 2c (active implantable medical device) of AIMDD.
    - MDs: Definition can be found in Article 1 (Definitions, scope) paragraph 2a (medical device) and 2b (accessory) of MDD.
    - IVDMDs: Definition can be found in Article 1 (Scope, definitions) paragraph 2a (medical device), 2b (*in vitro* diagnostic medical device), 2c (accessory) and 2d (device for self testing) of IVDMDD.
b) Make sure the exclusion clauses written in Article 1 of chosen directive is not relevant and applicable to the device
    - AIMDs: Check on the exclusion clauses written in paragraph 3 to 6 does not apply to the intended product such as the device purpose is more relevant to other directives available.
    - MDs: Check the device is not defined as AIMD or IVDMD and also it must not be applicable to the exclusion clauses stated in paragraph 2c to 2e and paragraph 3 to 6.
    - IVDMDs: Check on the exclusion clauses written in paragraph 3 to 7 does not apply to the intended product.

Step 2: Verify product essential requirements in Annex 1 or I ('Verify Requirements' in Figure 22)

a) Meet the general requirements and requirements in regards to the design and construction/ manufacturing process of the respective selected directive
b) Optional: Using relevant and applicable harmonized standards to demonstrate compliance in the product essential requirements

Step 3: Requires the involvement of notified body due to class/ category ('Involve Notified Body' in Figure 22)

a) Classify/ categorize the device
    - AIMDs: For all AIMDs are immediately considered as elevated risk devices which equivalent to Class III MDs in terms of risk level and therefore requirement for involving a notified body is compulsory in the later procedure.
    - MDs: For all devices that does not fall under the AIMDD or IVDMDD can be classified in accordance to Annex IX of MDD with the classes derived based on the rules (1 to 18) of the different medical devices. Figure 13 to 16 in the previous section shows the rules used to classify the devices into various classes. A notified body is compulsory to be involved for all classes except for Class I medical devices that do not require sterile and a measurement function.

- IVDMDs: For the devices that are listed in Annex II of IVDMDD and also designed for self-testing devices, it is necessary for a notified body to be involved due to the risk level.

b) Find suitable notified body that can perform checks with respect to the selected directive in Step 1. Perform a search on the database of New Approach Notified and Designated Organizations (NANDO) to select an appropriate notified body for the conformity assessment.

Step 4: Selection of conformity assessment route and declaration of conformity ('Select & Declare Conformity' in Figure 22)

a) Options for conformity assessment route

- AIMDs: To fulfill the AIMDs conformity assessment, the researcher has three routes to select from. The researcher can have the selected notified body to do either an inspection on the quality management system with an inclusive examination on the design (Annex 2) or an examination on the representative sample of the product (Annex 3) with a testing in the product batches (Annex 4) or inspection in the quality of the manufacturing process (Annex 5). For either route that the researcher has chosen, a certificate will be issued with an indication of the verified selected annex(es). Figure 23 shows the options available for AIMDs.

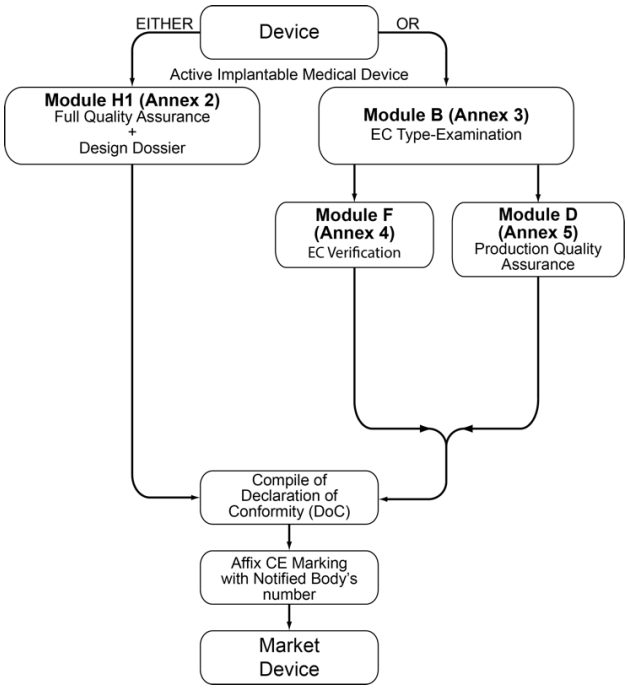


Figure 23 - Options available for assessment on AIMDs

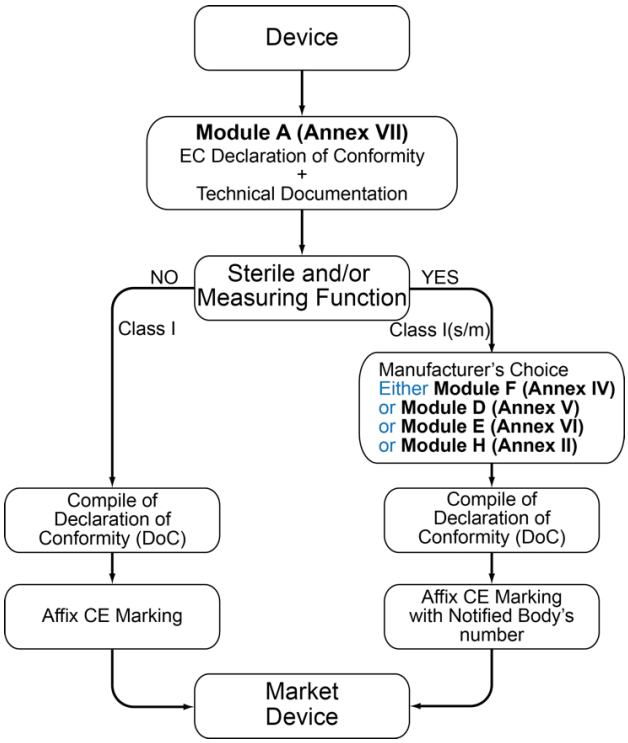


Figure 24 - Options available for assessment on MDs Class I, Im, Is

- MDs: To perform the MDs conformity assessment, the options available are linked directly with the class of the MDs. Class I MDs will have to do the technical documents (Annex VII) with or without the testing of batches (Annex IV), assurance of the quality in manufacturing process (Annex V) or product (Annex VI). For either route that the researcher has chosen, a certificate will be issued with an indication of the verified selected annex(es). Figure 24 shows the options available for assessment on Class I MDs.

  Class IIa MDs provides four routes where the first route does an inspection on the quality system without an examination in the design (Annex II). The other three available routes allow the researcher to prepare the technical documents (Annex VII) with either doing a batch testing (Annex IV), inspection of the quality in manufacturing process (Annex V) or product (Annex VI). For either route that the researcher has chosen, a certificate will be issued with an indication of the verified selected annex(es). Figure 25 shows the options available for assessment on Class IIa MDs.

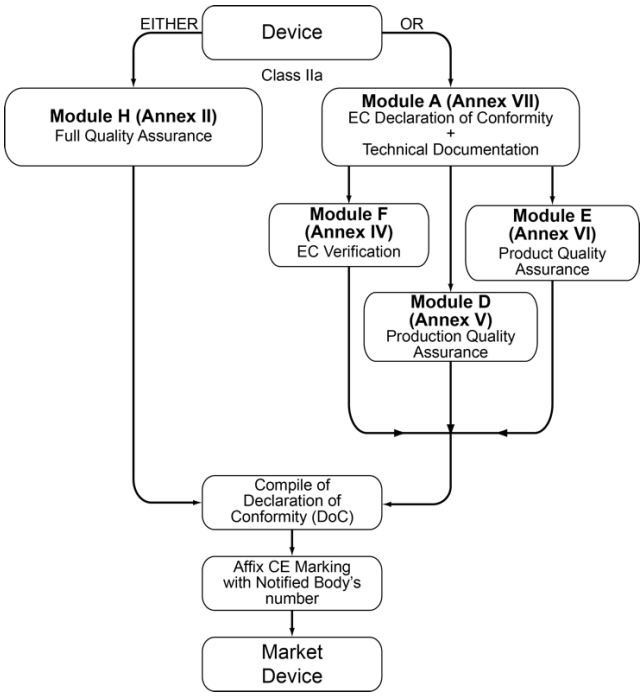


Figure 25 - Options available for assessment on MDs Class IIa

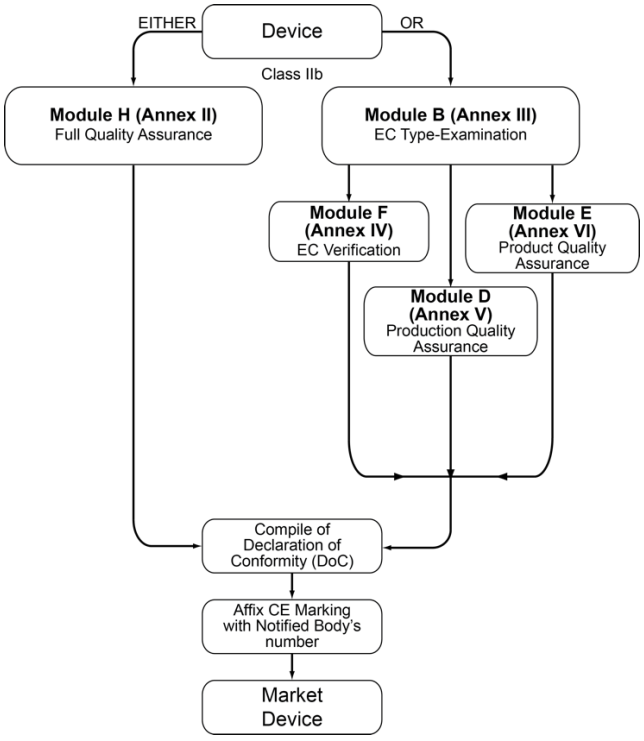


Figure 26 - Options available for assessment on MDs Class IIb

Class IIb MDs provides four routes where the first route does an inspection on the quality system without an examination in the design (Annex II). The other three available routes allow the researcher to do an examination on the representative sample of the product (Annex III) with either doing a batch testing (Annex IV), inspection of the quality in manufacturing process (Annex V) or product (Annex VI). For either route that the researcher has chosen, a certificate will be issued with an indication of the verified selected annex(es). Figure 26 shows the options available for assessment on Class IIb MDs.

Class III MDs have similar routes available as AIMDs. The conformity assessment routes available is to do either an inspection on the quality management system with an inclusive examination on the design (Annex II) or an examination on the representative sample of the product (Annex III) with a testing in the product batches (Annex IV) or inspection in the quality of the manufacturing process (Annex V). For either route that the researcher has chosen, a certificate will be issued with an indication of the verified selected annex(es). Figure 27 shows the options available for assessment on Class III MDs.

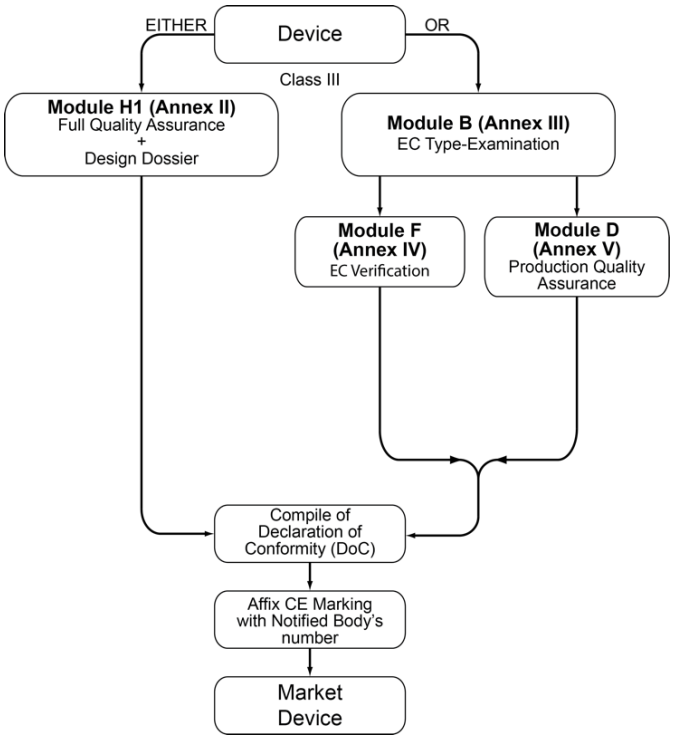


Figure 27 - Options available for assessment on MDs Class III

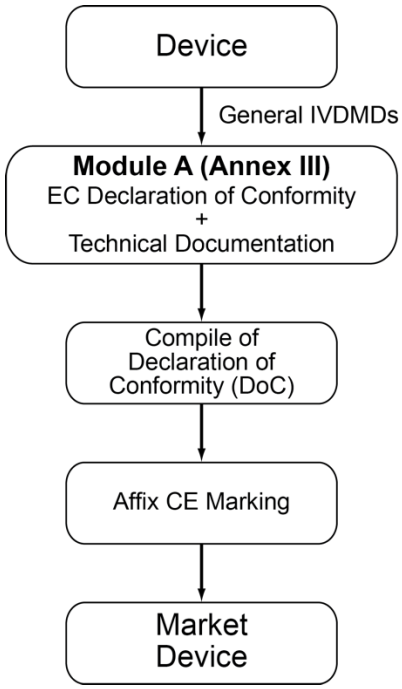


Figure 28 - Option for assessment on General IVDMDs

- IVDMDs: To perform the IVDMDs conformity assessment, the IVDMDs are based on category and each category provides two to three routes to choose from. For the general IVDMDs that are not list in Annex II, it required to do up technical documents and DoC (Annex III) and Figure 28 shows the route for general IVDMDs.

  For self testing IVDMDs, the simplest route is to do up technical documents and DoC (Annex III) unless it strictly requires to be check for quality (Annex II) or perform inspection representative sample (Annex V), batch testing (Annex VI) or checks on manufacturing process (Annex VII). Figure 29 shows the possible routes for self testing IVDMDs.

  For IVDMDs in List B, the device has three options where the first route focuses on the full inspection on the quality system (Annex IV) while the other focuses on inspection done to the representative sample (Annex V) and either perform a full batch testing (Annex VI) or inspect on the manufacturing process (Annex VII). Figure 30 shows the available options for IVDMDs in List B.

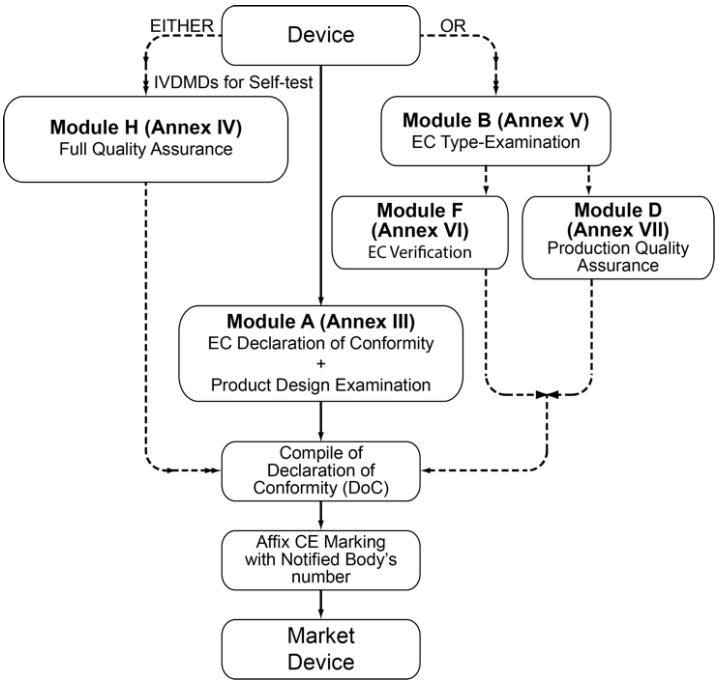


Figure 29 - Options available for assessment on Self testing IVDMDs

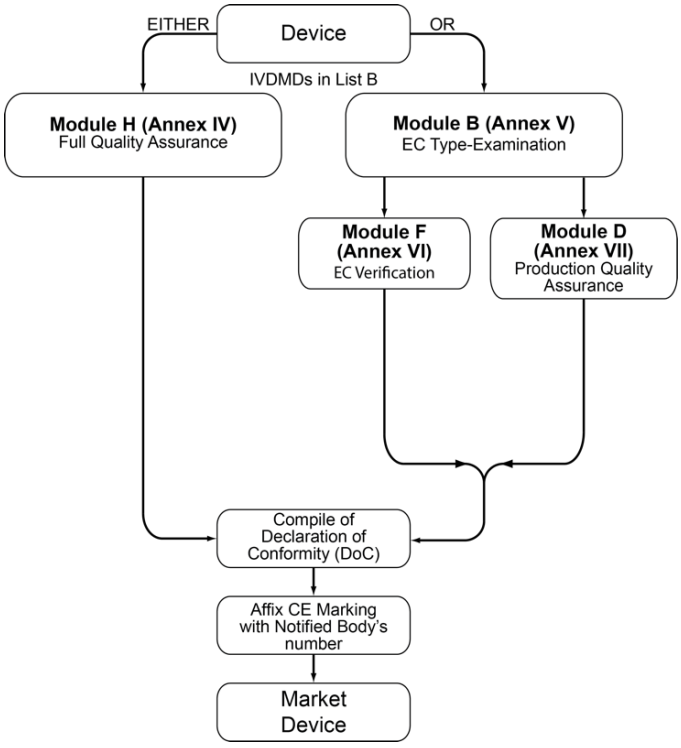


Figure 30 - Options available for assessment on IVDMDs in List B

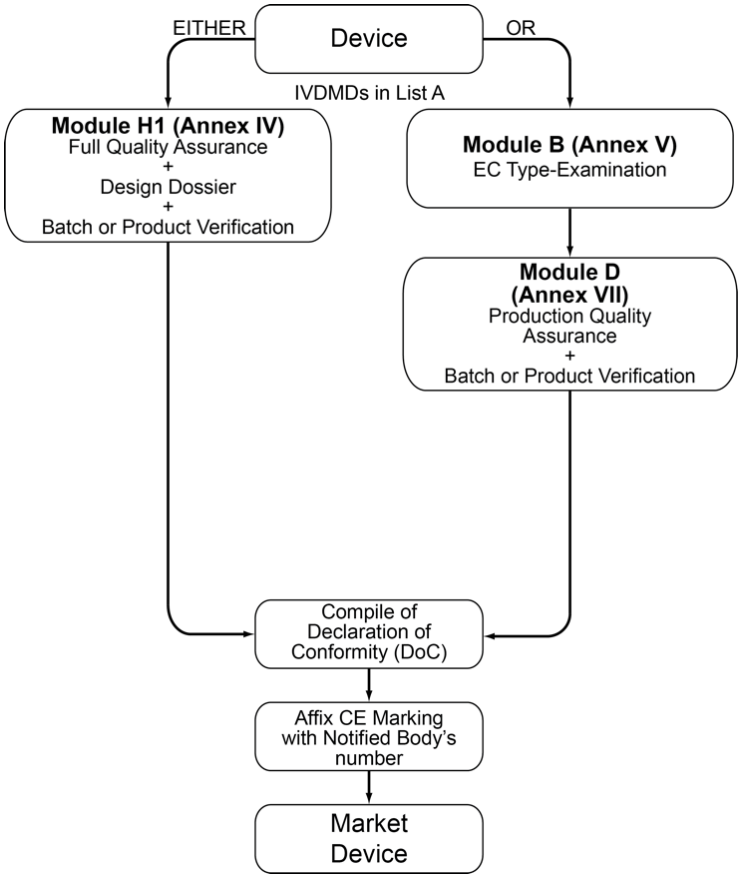


Figure 31 - Options available for assessment on IVDMDs in List A

For IVDMDs in List A, the device has two options where the first route focuses on the full inspection on the quality system (Annex IV) including design dossier and batch verification. The other route focuses on inspection done to the representative sample (Annex V) and a full batch testing and inspection on the manufacturing process (Annex VII). Figure 31 shows the available options for IVDMDs in List A.

b) Draw up Declaration of Conformity

In section 4.2.6,it is clearly highlighted that the document has to include information of the manufacturer such as the company name and place of business, the authorized representative particulars; the device details like name, type and/ or model; device class or category according to applicable directive; standards applied for proving of compliance; chosen conformity assessment route; notified body particulars including the identification number; place and date of issue; and lastly a signature of the manufacturer. The template can also be downloaded from the EU website and also shown in Appendix D1.

Step 5: Do up and maintain the availability of technical documents ('Technical Documentation' in Figure 22)

The researcher has to sort and come up with either a technical file or design dossier which is dependable on the class or category of the device. The contents required in the technical document are being described in the previous section 4.2.5 or the researcher can adopt the summary technical document (STED) format produced by the GHTF. It is a must that the manufacturer or the authorized representative maintains the availability of the technical documents for a minimum of either five years (MDs), ten years (IVDMDs) or fifteen years (AIMDs or implantable MDs).

Step 6: Attach and placement of CE marking ('Affix CE marking' in Figure 22)

The researcher has to make sure that dimension of the CE marking covered in section 4.2.7 is adhered accordingly. Depending on the available space and size of the device,

the CE marking can be affixed on the device or in the accompanying manual or both. Once this step is done, the device is ready to be marketed in the EU medical sector.

4.4 Summary

In this chapter, all the building blocks needed to design the CE medical decision model have been properly elaborated. With this seven building blocks and the steps of the various companies taken into consideration, a CE medical decision model is designed to combine these elements and factors or steps together to produce six simple steps for researchers to include in their product development phase. This CE medical decision model will allow the users to clear their uncertainty while planning to commercialize their product.

CHAPTER FIVE

CE MEDICAL DECISION MODEL WITH CASE STUDIES

5.1 Introduction

For this chapter of the thesis, three case studies will be used to demonstrate the practically and usefulness of the CE medical decision model. Each case study will be looking at a research product developed by either a research institution or institute of higher learning with the intended use on medical sector. With the use of these case studies as a form of demonstration, the decision made choosing on the most applicable route for the products shall be clearly shown with noteworthy aspects being discussed for better understanding.

5.2 Case Study 1: Wheelchair Gap Enabler

The first device to be introduced in the case study is a gap-clearing mechanism for wheelchair. The device was developed by Nanyang Technological University in 2006, a local research-intensive university with worldwide recognition in its engineering college focusing on innovations. The device was being funded by National Research Foundation (NRF) – Translational Research & Development (TRD) grant of S$130,000 with the aim to improve the quality of lives of the wheelchair users by allowing the occupants to cross gaps, small gutters or open drain easily. The invention, Wheelchair Gap Enabler, is made to be low-cost, lightweight and compact which allows it to be able to easily attached ono both inner sides of the maneuvering wheels and still maintain the existing functionality of a handrim-drive wheelchairs (US Patent No.

7644932, 2010). The device is mainly made up of aluminium for the structure and uses six inline skating wheels on each side and are attached onto the maneuvering wheels as shown in Figure 32.

Figure 32 - Wheelchair Gap Enabler

The device can be easily operated by simply rotating both of the operational handles, located at the front of the arm supports, towards the occupant. The wheel assembly will then be lowered down to the same level as the base contact point of the maneuvering wheels. This action will tilt the wheelchair and rotate the seat in the sagittal plane upwards while maintaining the seat to back support angle, putting the occupant into a

wheelie position (US Patent No. 7644932, 2010). This is shown in Figure 33 with the default position and the wheelie position of the wheelchair.

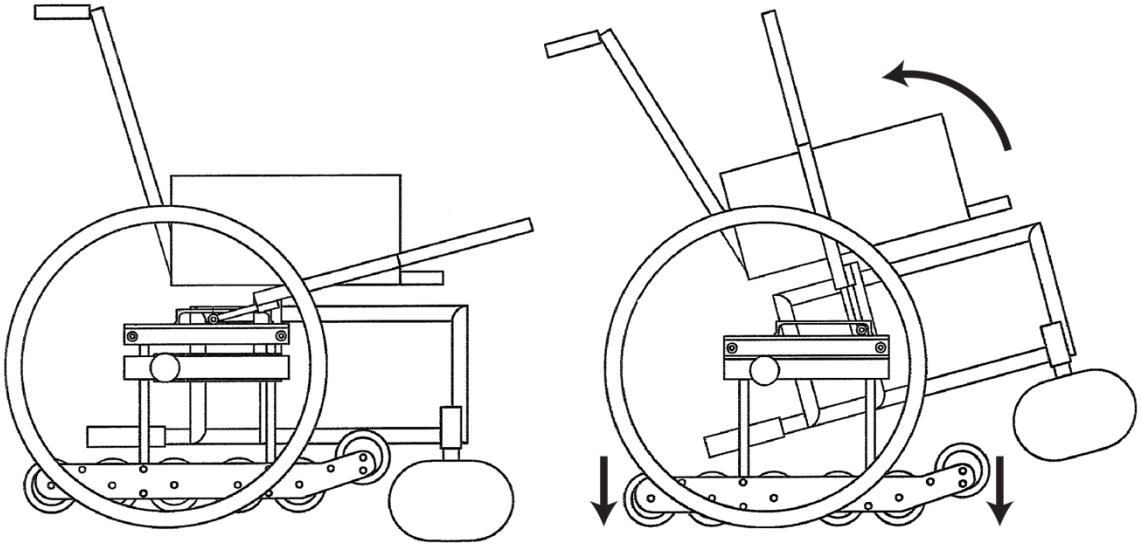


Figure 33 - Default position (Left) and Wheelie position (Right) of the wheelchair

Step 1: Identify applicable medical related directive(s) by definition & exclusion written in Article 1

Handrim-drive wheelchairs are commonly used in hospitals and nursing homes where the occupant is capable of using the handrims to maneuver the wheelchair and does not require the help from an assistant. The device is not being powered by electrical means, cannot be implanted to human body and does not do any form of specimen diagnoses so it cannot be an active implantable device or an *in vitro* diagnostic device. Therefore, the most applicable directive for the device can only be the medical device directive (MDD).

With reference to the MDD and according to the definition stated in Article 1 (Scope, definitions), the most applicable definition for the device is to be considered as an accessory to a medical device as the Wheelchair Gap Enabler is an attachment to the existing wheelchairs. Accessory, with reference to paragraph 2b, can be defined as not a device but is used in hand or together with a medical device and having its original intended usage remain unchanged. The device is not applicable to be either in the medicinal products or cosmetic products stated in Article 1 paragraph 3 to 6 of MDD.

Step 2: Verify product essential requirements in Annex 1 or I

In Annex I of the MDD, the requirement which is more applicable to the device will be the construction and environmental properties. It states that the device which is used in combination with other medical devices must be safe and not restrict the specific functions of the medical devices. The device must also be designed and manufactured without or with minimal risk of injury in accordance to the appropriate ergonomic features.

Standard EN 12183:2014 (Manual wheelchairs: Requirements and test methods) describes the prerequisites and test methods for any manual wheelchairs that are designed to carry a person of mass less than 250 kg (BSI, 2014). The standard covers from the test preparation to the different test available such as wheelchair performance, component properties, propulsion and braking systems and also operations of the wheelchairs. The most suitable testing method for the device are the tilting fatigue strength under the Wheelchair Performance section and Seating adjustments for tilt and recline systems under Operations section.

Test 1: Tilting fatigue strength

Occupied wheelchairs can often be tipped backwards when maneuvering them. The tipping action can put considerable stress on the back support and related components. It is important that a manual wheelchair that can be tipped in this way is able to withstand repeated tipping without damage.

Requirement

This requirement applies only to wheelchairs where the maximum occupant mass is not greater than 150 kg and where the intended use includes tipping the occupied wheelchair backwards about the rear wheel axles by use of the push handles.

After the wheelchair has been subjected to the test method, no part of the back support shall be movable from the preset position and also no assembly of parts or component shall display any noticeable crack signs, fractures, free play, occurrence of deformations, lack in controlled tuning or any other damage that severely affects the function of the wheelchair.

Test method

a) If the position of the rear wheels is adjustable, set them to the most rearward position with regards to the manufacturer's instructions for use. If the position of the front wheels is adjustable, set them to the most forward position with reference to the manufacturer's instructions.
b) If the position of the back support and/or push handles is adjustable, set them to the maximum height according to the manufacturer's instructions.
c) Ensure that the rear wheels are free to rotate, for example by disengaging parking brakes.

d) Restrain the rear wheels using appropriate means so that the wheelchair can be tipped about the axles of the rear wheels without the wheels moving.

e) Attach the means to tip the wheelchair to the push handles so that it will apply forces in a vertical plane parallel to the forward direction of movement that will be divided equally to the wheelchair. Make sure the means of attachment cannot apply any lateral forces to the push handles.

f) Secure the dummy in the wheelchair using appropriate means so that it will remain in position as the wheelchair is tipped and returned to the upright position.

g) Using the means to tip the wheelchair, smoothly tip the loaded wheelchair backwards to the point of balance (where the center of mass of the loaded wheelchair is directly above the rear axles), ± 1°, or to the angle where the front wheels are lifted to a height of $120\ ^{+10}_{0}$ mm above the test surface, whichever angle is greater. Then smoothly return the loaded wheelchair to the upright position. Ensure the push handles are not pushed forward when the wheelchair is upright.

h) Repeat g) for 20 000 cycles at a rate of $10\ ^{+2}_{0}$ cycles per minute.

i) Inspect the wheelchair and determine whether it has met the requirement.

Test 2: Seating adjustments for tilt and recline systems

Requirements

If the manufacturer states that the seating position of the wheelchair can be adjusted by the occupant while he/she is seated, he/she shall not have to lift a total mass of both the seating and occupant which presents a safety hazard in moving and handling to the occupant.

Controls or operating handles for the adjustable seating meant to be controlled by the occupant has to be reachable to the occupant in all the available seating positions.

Test method

a) Change the seating in accordance with the manufacturer's instructions of use.
b) Note down if the wheelchair has met the necessary requirements.

Test report

Each of the test that is being carried out should provide a test report that includes the following elements:

a) a unique report number;
b) the testing institution’s name and address;
c) the issuing date of the test report;
d) a reference to the European Standard EN 12183:2014;
e) the manufacturer’s name and address;
f) a description of the sample which includes the manufacturer's trade mark, model, unique identification number and the available accessories attached;
g) the source of the sample;

h) details of the set-up of the wheelchair including how it is equipped and details of adjustments;

i) the mass of the dummy used;

j) the test results;

Step 3: Requires the involvement of notified body due to class/ category

With reference to Part III (Classification) stated in Annex IX (Classification criteria), the most applicable path for the device to follow will be the path for non invasive devices. Under the non invasive devices path of Annex IX, the suitable classification of device will be to follow Rule 1 as stated that as long as the device does not touch or come into contact with the patient's skin. Wheelchair are medical devices generally used as a form of support to patient so does the accessory (the device) that is meant to attached to the wheelchair. Therefore, according to Rule 1 of Annex IX, the device can be classified as a Class I device of low risk under the MDD. Figure 34 shows the classification path of the Wheelchair Gap Enabler.

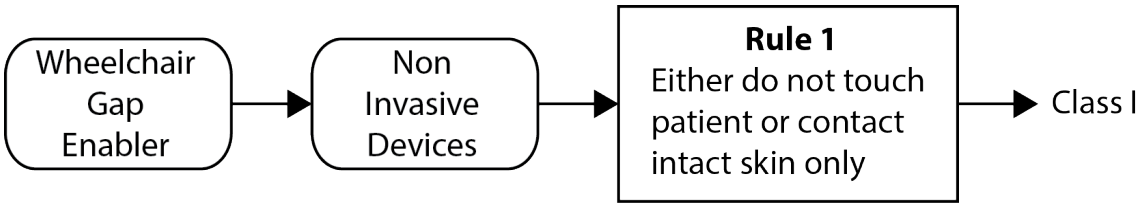


Figure 34 - Classification path of Wheelchair Gap Enabler (Rule 1)

The involvement of a notified body is unnecessary for the Class I device as it does not have any measuring function or requires to be in a sterile condition when placed on market.

Step 4: Selection of conformity assessment route and declaration of conformity

There are a total of six conformity assessment procedures (Annex II to VII) available for medical devices to conform to in the MDD. The device is being classified as a Class I device according to Step 3 and it does not consist of a measuring function or require sterilization before placing it on the market. The device will follow Section 2 of Annex VII with reference to paragraph 5, Article 11 of MDD in the preparation of the technical documentation to support the declaration of conformity (DoC). Figure 35 shows the chosen conformity route for the Wheelchair Gap Enabler.

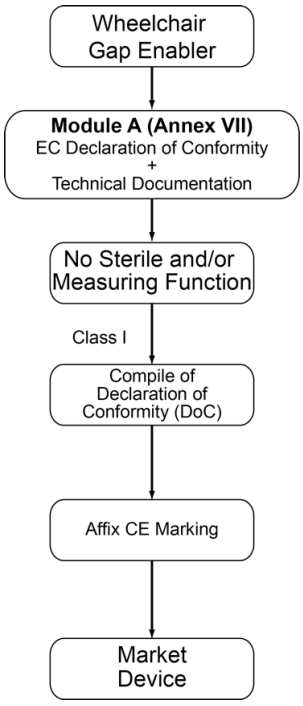


Figure 35 - Conformity Route (Annex VII) for Wheelchair Gap Enabler

SYSTEMED Advancing Innovation Enhancing Life	**DECLARATION OF CONFORMITY**

Manufacturer: SysteMED Pte Ltd
Innovation Centre
16 Nanyang Drive, Block 1, Unit 206
Singapore 637722
Tel: +65 8183 2781

Notified Body: Not Applicable

European Representative: Emergo Europe
Molenstraat 15
2513 BH, The Hague
The Netherlands
Tel: +31 (0) 70 345 8570
Fax: +31 (0) 70 346 7299

Medical Device(s):

1. Wheelchair Gap Enabler

We herewith declare that the above-mentioned product meets the provisions of the Council Directive 93/42/EEC (MDD). All supporting documentation is retained under the premises of the manufacturer.

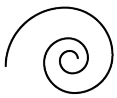
Device Classification: Class I (Rule 1), non-invasive device

Standards Applied: EN 12183:2014

Decision according to Annex VII of Council Directive 93/42/EEC concerning medical devices

Place: SysteMED Pte Ltd, Singapore

Date: Month Day, Year (e.g. November 12, 2015)

Signature: 

Name: XX XX XXXX
Director of SysteMED Pte Ltd

Figure 36 - Declaration of Conformity for Wheelchair Gap Enabler

With no necessary involvement of notified body for the device, a Declaration of Conformity (DoC) has to be compiled and drawn up as a declaration of the manufacturer's responsibility towards the conformity of the MDD. The necessary details needed are manufacturer's details such as name and address, important features of the product as well as a compulsory signature of the organization. The requirement of an authorized representative (EC Rep) is needed for the device to be sold in Europe and the selected EC Rep is Emergo Europe. Figure 36 show a mock version with necessary details of the DoC that needs to be drawn up for Wheelchair Gap Enabler.

Step 5: Do up and maintain the availability of technical documents

The technical document will have to include the DoC of Figure 36, risk analysis report referencing to ISO 14971, mechanical construction data including drawings and explanation, etc. Figure 37 shows an example of the mechanical drawings of the Wheelchair Gap Enabler that will be included in the technical documents. Given that the device is being developed out of the European Union countries (in Singapore), the appointed authorized representative (Emergo Europe) has to keep a duplicated copy of the actual technical documents provided by the manufacturer with a duration of no less than 5 years when the device is available in the EU market.

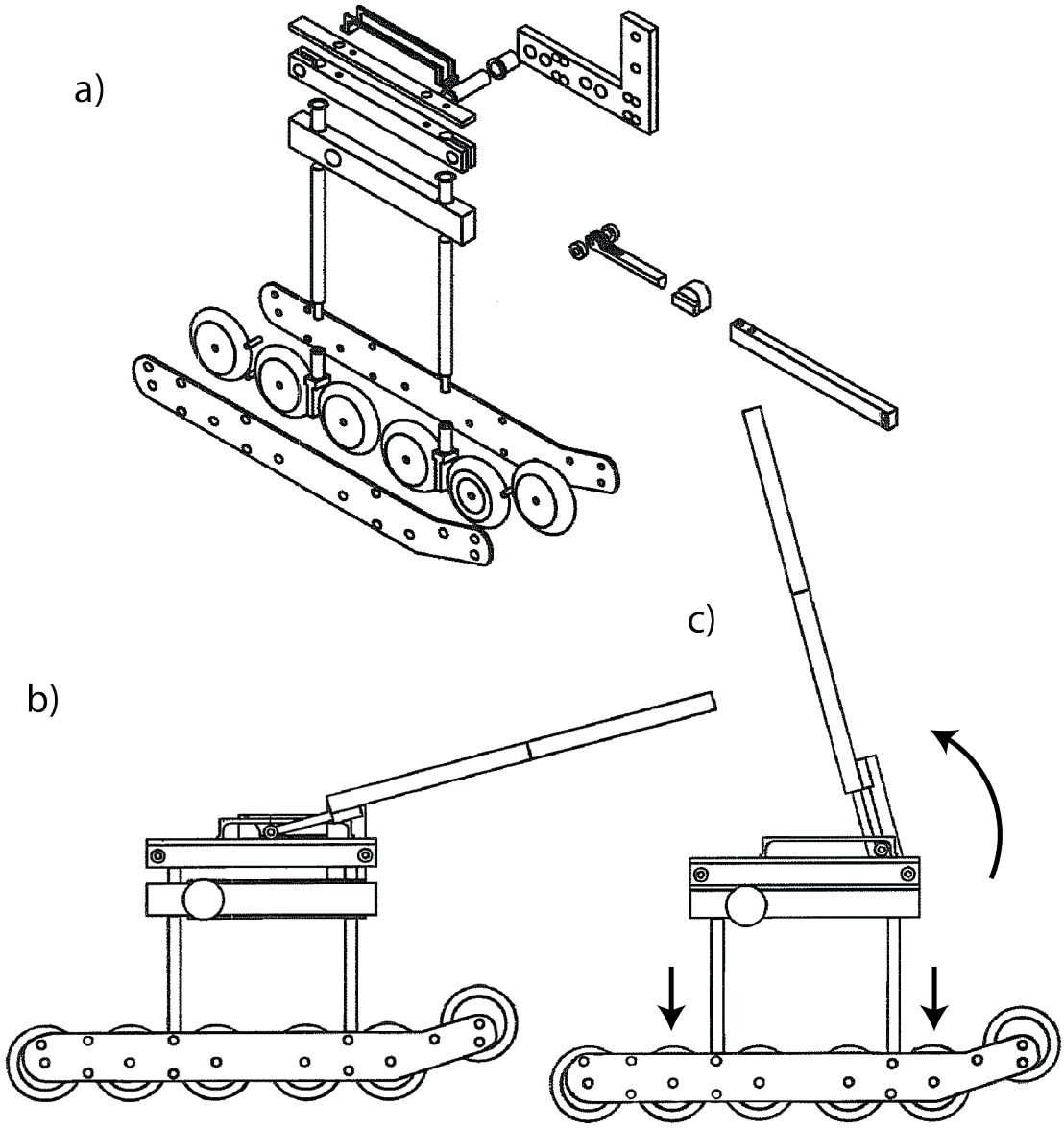


Figure 37 - Mechancial drawings of Wheelchair Gap Enabler. a) Exploded view, b) initial position, c) final position

Step 6: Attach and placement of CE marking

After the compilation of the technical document is done in Step 5, only then can the CE marking be affixed onto the device and be marketed as a medical device in the

European community. The device does not have a proper or visible space to place the CE marking with a minimum height of 5 mm so an alternate solution is to place on the packaging and the accompany document like the instruction of use. It is stated clearly in Step 3 that there is no involvement of notified body in performing the conformity assessment option (Annex VII) stated in Step 4, therefore no identification number is needed to be displayed on the packaging and accompany document.

5.3 Case Study 2: Synergistic Physio-Neuro (SynPhNe) Platform

The second device to be introduced in the case study is a physio-neuro stroke rehabilitation system. The Synergistic Physio-Neuro (SynPhNe) platform/ system was developed by Nanyang Technological University in 2012 with several sources of funding such as from Proof-of-Concept (POC) grant of S$250,000 by National Research Foundation (NRF). The SynPhNe system aims to assist patients who suffers from stroke on the upper limbs or have minor brain injuries in their recovery process (US Patent No. 2014/0200432, 2014). The whole rehabilitation system consists of a couple of devices: a wired headset with electroencephalogram (EEG) sensors that senses electrical activities in the brain, a wired arm band/ glove with surface electromyogram (sEMG) sensors that senses electrical activities of the skeletal muscles and lastly a patented computer software that records and stores the electrical activities and provides real time feedback to the users on the rehabilitation progress (Banerji S. , Heng, Ponvignesh, & Menezes, 2013). Figure 38 shows the overview of the stroke rehabilitation system (SynPhNe).

Figure 38 – Overview of the SynPhNe System

The neuro (EEG) headset and the sEMG arm glove can be easily worn by stroke patients with the ability to control only a single arm. These two devices will be connected to a data capturing unit which is wearable to the users and the captured electrical activities will be converted to signals and transmit to the training platform (Computer) (Banerji S. , Heng, Ponvignesh, & Menezes, 2013). The training platform will be installed with the patented software which will responsible for displaying a series of instructional videos for the patients to follow the exact same move and improve their performance. Figure 39 shows the flow of signals and devices that made up of the SynPhNe system.

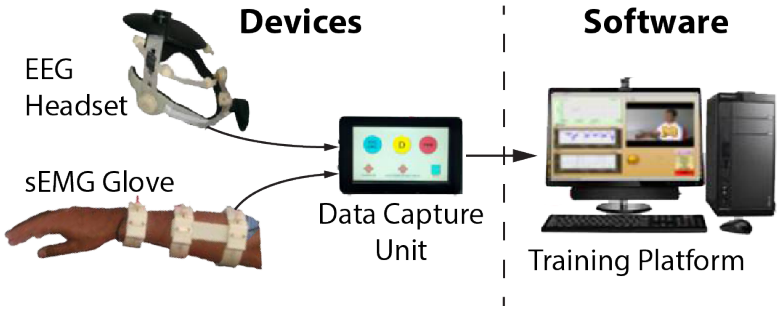


Figure 39 - Flow of signals and devices in the SynPhNe system

Step 1: Identify applicable medical related directive(s) by definition & exclusion written in Article 1

The SynPhNe system comprises of three main modules which are an EEG headset, a sEMG arm glove and a customized software. The whole system needs to be powered by electrical means and it does provide feedbacks in the form of data related to the patient/ wearer. The system cannot fall under the active implantable medical device directive(AIMDD) because both the EEG headset and sEMG arm glove are not meant to be implantable but only touch the surface of the wearer's skin. The system also cannot be under the *in vitro* diagnostic medical device directive (IVDMDD) because it does not perform any specimen examination. Therefore, the most applicable directive for the whole system in this case study will be the MDD.

With reference to MDD and according to the definition stated in Article 1 (Scope, definitions), the most applicable definition for the system is the definition of medical device stated clearly in paragraph 2a. Medical device, with reference to paragraph 2a, states that any instruments with the combination of software used specifically for therapeutic or rehabilitation purposes are to be consider as a medical device. The

system also requires the use of electrical source to power up the devices so it is an active medical device. The system does not have any medicinal usage nor can it be considered as a cosmetic product as stated in Article 1 paragraph 3 to 6 of MDD.

Step 2: Verify product essential requirements in Annex 1 or I

In Annex I of the MDD, the requirements which are relevant to the system will be paragraph 10 (devices with a measuring function) and paragraph 12 (Requirements for MDs equipped with or connected to an energy source). Under the devices with a measuring function section, it is stated that the devices are required to be able to provide accuracy within the specified limits of the accuracy intended by the devices and it must also be specified by the manufacturer. The recorded measurements shall be in the units which conforms to the EU Metric Directive.

Under the section of MDs connected to or equipped with an energy source, it is a must to guarantee the repeatability and consistency of the performance in the devices. The software used must also be validate with reference to the principles of development lifecycle. The devices that are used to monitor the patient's brain and muscles signals have to include the alarming functions in order to alert personnel on any power failure. The instructions provided by the software through visual means have to be understandable by the patient or user.

Standard EN 60601-2-26:2015 (Medical electrical equipment: Particular requirements for the basic safety and essential performance of electroencephalographs) describes the fundamental safety and required performance of electroencephalographs used in clinical environment (BSI, 2015). This standard mainly covers the protection criteria

against hazards that are mechanical, electrical and environmental related. There are two relevant essential performance requirements for the EEG headset to fulfill: Accuracy of signal reproduction and frequency response.

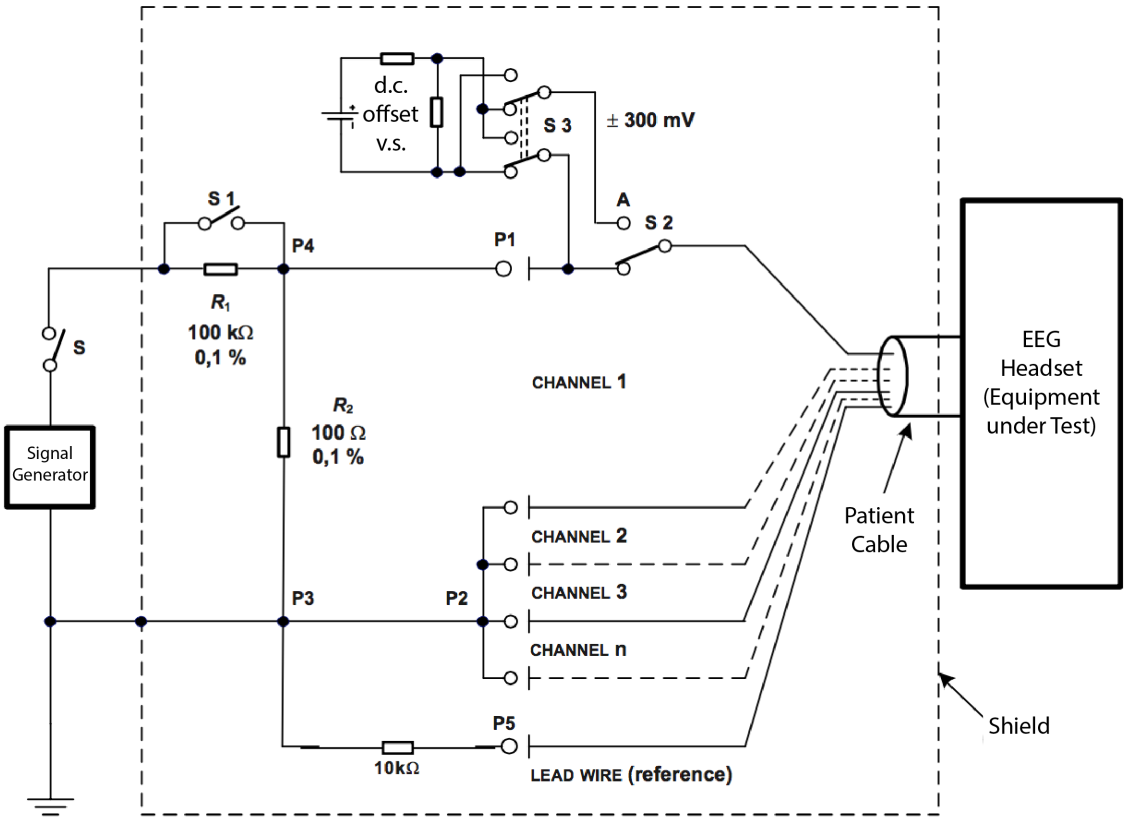


Figure 40 - Testing Circuit for Electroenphalographs (EEG)

Accuracy of Signal Reproduction

Input signals in the range of ±0.5 mV, changing at 12 mV/s, shall be reproduced on the output with an error of ≤ ±20 % of the nominal value of the output or ±10 µV, whichever is greater. Compliance is checked using the testing circuit for EEG as shown in Figure 40.

Close the switch S and S2 and connect up the signal generator to apply a triangular wave of 2 Hz to any lead wire of a channel with all other lead wires connected to the reference lead wire. Adjust the gain of the EEG headset to 0.1 mm/μV. Adjust the signal generator to produce a peak-to-valley output on a display device that is 10 % of the full scale peak-to-valley output. Increase the output of the signal generator by factors of 2, 5 and 10. The displayed output shall be linear within ±20 % of the full scale output. Repeat for each lead wire of the available channels until all combinations of lead wires have been tested.

Connect the signal generator to any lead wire of a channel with all other lead wires connected to the reference lead wire. Adjust the signal generator to apply a 1 mV peak-to- valley input 6 Hz triangular signal at a gain of 0.01 mm/μV. Verify that the output display is completely visible and the peak-to-valley amplitude is within (8 to 12) mm.Repeat for each lead wire of the available channels until all combinations of lead wires have been tested.

Frequency Response

The EEG headset shall meet the requirement for a frequency response (bandwidth) of at least 0.5 Hz to 50 Hz when tested with sinusoidal input signals. The output at 0.5 Hz and 50 Hz shall be within 71 % to 110 % of the output obtained with a 5 Hz sine wave input signal.

Compliance is checked using the test circuit of Figure 40. The mains frequency notch filter, if provided, and filter settings are to be off for this test.

Close switches S and S2. Adjust the gain of the EEG headset to 0,05 mm/μV. Use the signal generator to apply a 5 Hz, 200 μV peak-to-valley sine wave signal between any lead wire of a channel with all other lead wires connected to the reference lead wire. Verify that at 0.5Hz and 50Hz, the amplitude of the output signal remains in the range of 71 % to 110 % compared to the frequency of 5 Hz.

Step 3: Requires the involvement of notified body due to class/ category

The SynPhNe system has three different medical devices where two of them are hardware devices and one is a customized software. For the first device (EEG headset) referencing to Part III (Classification) in Annex IX (Classifcation criteria), the most relevant path for the EEG device is to follow the active devices path. Under the active devices path, the suitable classification of the EEG device will be to follow Rule 10 as it is an active device to be used to do direct monitoring of the vital physiological parameters of the human body.

For the second device (sEMG arm glove) referencing to Part III in Annex IX, the most relevant path for the sEMG device is to follow the active devices path. Under the active devices path, the suitable classification of the sEMG device will be to follow Rule 12 as the device is an active device but does not administer or supply energy (Rule 9) or monitoring vital physiological parameters of the human body (Rule 10) or removal of body liquids (Rule 11).

For the customized software referencing to Part II (Implementing rules) in Annex IX, it is stated in point 2.3 where the software will automatically fall under the same class of the higher class device. By treating the whole system as one device with reference to

point 2.5 of Part II in Annex IX, the higher class rule shall apply to the device when several rules are applicable. Therefore, the SynPhNe system shall be classified as a Class IIa medical device according to Rule 10 of MDD. Figure 41 shows the classification path of the SynPhNe system.

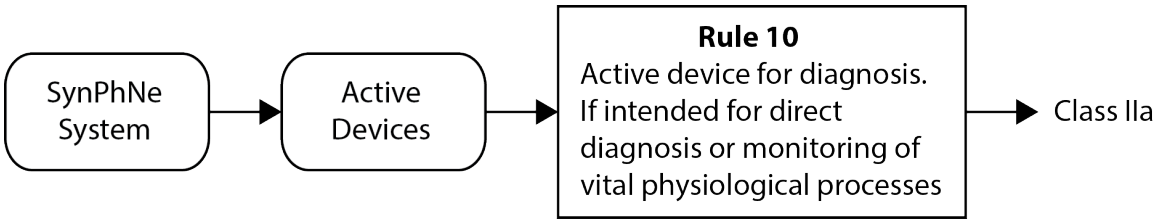


Figure 41 - Classification path of SynPhNe System (Rule 10)

With the selected directive to be MDD in Step 1, the available notified bodies can be found from the database of NANDO or in Appendix A3. Assuming that the chosen notified body to be BSI Group (NB 0086) from United Kingdom, BSI will be responsible for the inspection of the chosen conformity assessment option in Step 4.

Step 4: Selection of conformity assessment route and declaration of conformity

The SynPhNe system has been classified as a Class IIa device according to Step 3. With reference to Article 11 paragraph 2 of MDD, there are four possible routes which the researcher can choose from:

1) Route 1: according to Annex II (Full quality)
2) Route 2: according to Annex VII in combination with Annex IV(Verification)
3) Route 3: according to Annex VII in combination with Annex V (Production)

4) Route 4: according to Annex VII in combination with Annex VI (Product)

Route 1 is not looked into as it is the easiest but costly route for researchers with limited budget to commercialize their product. Route 2 has Annex IV that deals with statistical verification of products and is recommended for products manufactured in mass production so it is not a suitable route for the SynPhNe system. Route 3 has Annex V that deals with the inspection and quality of the manufacturing stages which in particular regards to the sterilization of the product. Route 4 has Annex VI that deals with the examination of each product or a representative sample of each batch. Comparing Route 3 and Route 4, the procedure according to Route 3 is more relevant to be conducted for the SynPhNe system as the manufactured EEG headsets and sEMG arm gloves have to be properly sterilized during the manufacturing process. Thus the route according to Annex VII in combination with Annex V is suitable for the SynPhNe system of Class IIa. Figure 42 shows the chosen conformity route for the SynPhNe system.

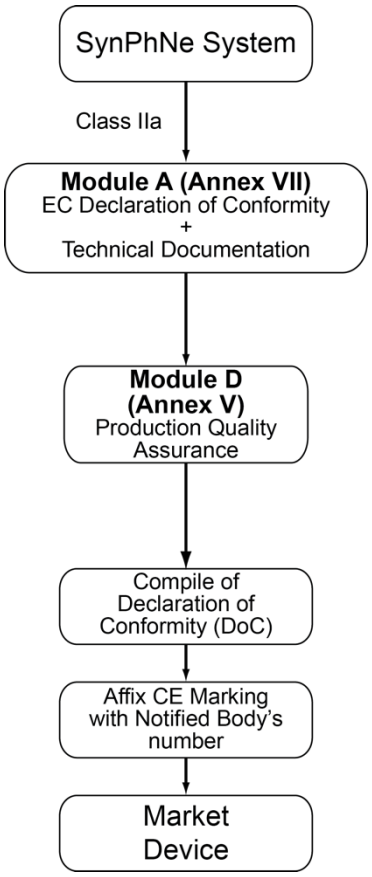


Figure 42 - Conformity Route (Annex VII & Annex V) for SynPhNe System

The assessment of the conformity route, Annex V, will be inspected by the chosen notified body, BSI Group, in Step 3. During the inspection of the conformity route, the researcher can start to compile and do up the conformity declaration document with the necessary information. The requirement of an authorized representative (EC Rep) is needed for the device to be sold in Europe and the selected EC Rep is Emergo Europe. Figure 43 show a mock version with necessary details of the DoC that needs to be drawn up for SynPhNe system.

SynPhNe™	DECLARATION OF CONFORMITY

Manufacturer:
SynPhNe Pte Ltd
Innovation Centre, Block 1,
16 Nanyang Drive
Singapore 637722
Tel: +65 8183 2781

Notified Body:
BSI
Kitemark Court Davy Avenue Knowhill
Milton Keynes MK5 8PP, United Kingdom
Tel: +44 (0) 8450 809000
Fax: +44 (0) 8450 809000

European Representative:
Emergo Europe
Molenstraat 15, 2513 BH, The Hague
The Netherlands
Tel: +31 (0) 70 345 8570
Fax: +31 (0) 70 346 7299

Medical Device(s):

1. SynPhNe Platform System

We herewith declare that the above-mentioned product meets the provisions of the Council Directive 93/42/EEC (MDD). All supporting documentation is retained under the premises of the manufacturer.

Device Classification: Class IIa (Rule 10), non-invasive, active device

Standards Applied:
EN 60601-1:2006
EN 60601-2-26:2015

Decision according to Annex VII and Annex V (production quality assurance) of Council Directive 93/42/EEC concerning medical devices.

Place: SynPhNe Pte Ltd, Singapore

Date: November 12, 2015

Signature:

Name:
Dr John Heng
Director of SynPhNe Pte Ltd

Figure 43 - Declaration of Conformity for SynPhNe System

Step 5: Do up and maintain the availability of technical documents

The technical document will have to include the DoC of Figure 43, risk analysis report referencing to ISO 14971, clinical trial data, mechanical and electrical construction data including drawings and explanation, etc. Given that the device is being developed out of the European Union countries (in Singapore), the appointed authorized representative (Emergo Europe) has to keep a duplicated copy of the actual technical documents provided by the manufacturer with a duration of no less than 5 years when the device is available in the EU market.

Step 6: Attach and placement of CE marking

After the compilation of the technical document is done in Step 5, only then can the CE marking be affixed onto the device and be marketed as a medical device in the European community. The SynPhNe system does have visible space on the exterior of both EEG headset and sEMG arm gloves to place the CE marking and also on the packaging and the accompany document like the instruction of use. It is stated clearly in Step 3 that there is an involvement of notified body, BSI Group, in performing the conformity assessment options (Annex VII and Annex V) stated in Step 4, therefore the identification number CE0086 is needed to be displayed on the devices, packaging and accompany document.

5.4 Case Study 3: Ankle Brachial Index (ABI) Device

The third device to be introduced in the case study is a portable and standalone screening device to detect peripheral arterial disease (PAD). The device was developed by Ngee Ann Polytechnic in 2014, a local institution of higher learning (IHL) in providing education for diploma courses and also does focus on research and development work in the bioscience & technology area. The development of the device was being funded by Tote Board Social Innovation Research (SIR) fund of S$120,000 with the aim to provide a painless and time saving measurement for the patients during their visit for the PAD examination. The current PAD examination is done to help screen for blockage in the lower limbs arteries with the use sphygmomanometer &ultrasound Doppler technique that requires the use of multiple equipment, time consuming setup and uncomfortable measurement by the pressure cuffs. The ankle brachial index (ABI) device made to be low-cost and portable which allows the healthcare workers to carry around easily when taking the measurements. Figure 44 shows the ABI device that is developed for the examination of PAD.

Figure 44 - ABI Device for peripheral arterial disease (PAD) examination

The ABI device consist of three main modules that are incorporated together: an electrocardiogram (EEG) module that senses the electrical activity of the heart, four photoplethysmogram (PPG) modules that senses the relative blood flow in the four limbs and finally a software that will analyze the readings for the five sites and indicate the ankle brachial index of the patient (Tan, Chua, & Foo, 2014). The PPG sensors that can be used are commonly found in hospital so it is not included with the ABI device. Figure 45 shows the technique difference in the current technique of sphygmomanometer & ultrasound Doppler and the developed technique of the ABI device.

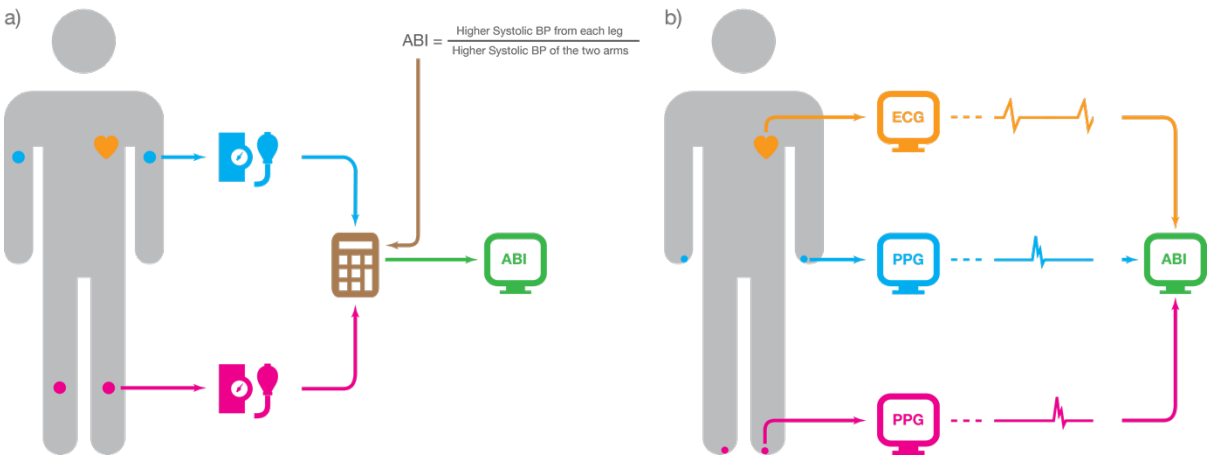


Figure 45 - Technique difference in Sphygmomanometer & Ultrasound Doppler (Left – a) and ABI Device (Right – b)

Step 1: Identify applicable medical related directive(s) by definition & exclusion written in Article 1

The ABI device consists of two functions which are the ECG module and PPG module and an incorporated software. The device requires the use of electrical means which can be from the battery or power source and it does provide simple information such as heart rate and the ABI value. The device does not require to be implant into the human body nor does it perform any specimen diagnoses. Therefore, the device cannot be under the AIMDD nor the IVDMDD but the applicable directive will be MDD.

With reference to MDD and according to the definition stated in Article 1 (Scope, definitions), the most applicable definition for the device is to be considered as a medical device. Medical device, with reference to paragraph 2a, define that any instruments used alone for diagnosis or monitoring of disease are considered as medical devices. The device also requires the use of electrical source to power up itself so it is an active medical device. The device does not contain any medicinal usage nor can it be used for cosmetic purpose as stated in Article 1 paragraph 3 to 6 of MDD.

Step 2: Verify product essential requirements in Annex 1 or I

In Annex I of the MDD, the requirements which are relevant to the system will be paragraph 10 (devices with a measuring function) and paragraph 12 (Requirements for MDs equipped with or connected to an energy source). Under the devices with a measuring function section, it is stated that the devices are required to be able to provide accuracy within the specified limits of the accuracy intended by the devices and it must also be specified by the manufacturer. The recorded measurements shall be

in the units which conforms to the EU Metric Directive. Under the section of MDs connected to or equipped with an energy source, it is a must to guarantee the repeatability and consistency of the performance in the devices.

Standard EN 60601-2-25:2015 (Particular requirements for the basic safety and essential performance of electrocardiographs) describes on the safety and performance requirements of electrocardiographs used in clinical environment (BSI, 2015). This standard covers the protection criteria against hazards that are mechanical, electrical and environmental related. There are two relevant requirements in the reduction of effects of unwanted external voltages for the ECG module.

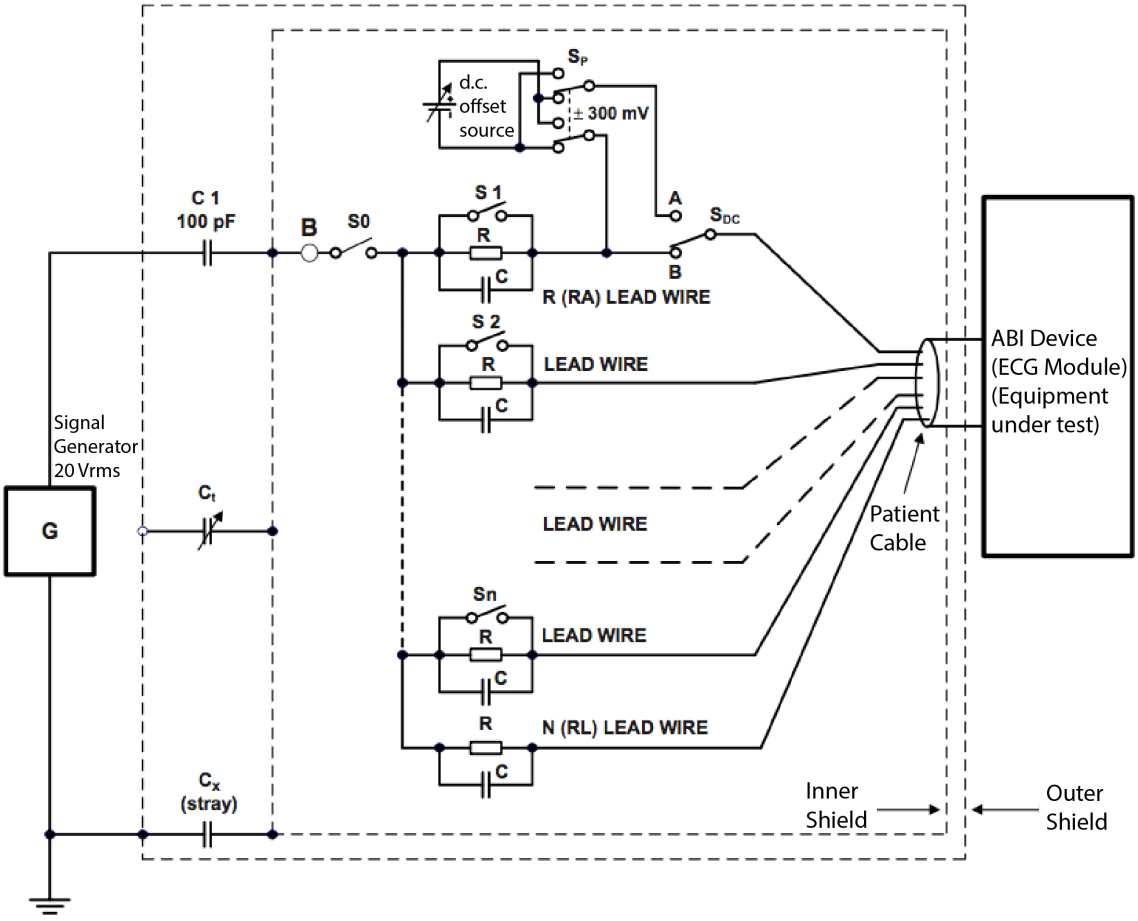


Figure 46 - Testing circuit for Common Mode Rejection and Noise level

Common Mode Rejection

A 10 V r.m.s. signal at mains frequency with 200 pF source capacitance, connected between earth and all lead wires connected together shall not produce an output signal greater than 10 mm peak-to-valley with the setting of gain 10 mm/mV for not less than 15 seconds. Each electrode shall be connected in series with one 51 kΩ resistor and parallel with one 47 nF capacitor. The patient cable specified by the manufacturer shall be used.

Compliance is checked using the test circuit of Figure 46 and a ruler or calipers accurate to within 0.2 mm. The test has to be performed with main frequencies of 50 Hz and 60 Hz.

a) Adjust C_t to produce 10 V r.m.s. at mains frequency at point B, while no patient cable is attached (S0 open). The common mode voltage applied to the ECG module is then 10 V rms. Ensure that the notch filter is switched off for this test, even if this needs any special method or software to access the control related to the filter.

b) Close switches S0 and S2 through S_n, open S1, and set S_{DC} to position B. Tune the gain to 10 mm/mV and the sweep speed to 25 mm/s. Measure the output amplitude for not less than a period of 15 seconds at that gain setting. Then open S2 and close all other switches. Repeat the amplitude measurement. Continue until the measurement has been made with all lead wires.

c) The test will be repeated with +300mV d.c. and –300mV d.c. offset voltage in series with the imbalance impedance, by setting S_{DC} to position A and testing with switch S_P in each of its two positions.

The resulting values shall not be greater than 10 mm peak-to-valley. Ensure that the line frequency notch filter (if provided) is turned off for this test, even if this requires special software or a special method of accessing the control over that filter.

In Figure 46, C_1 and C_t mimic the capacitance of the patient to ground. The inner shield reduces the pickup of unwanted extraneous signals. The capacitance C_x between the external and inner shields have effects on both the common mode voltage and source capacitance, a trimmer capacitor will increase the capacitance to 100 pF, equivalent to the capacitor of the generator, C_1. The output of the generator is then raised to 20 V r.m.s, thus giving a 10 V r.m.s at the common mode point B with a source impedance of 200 pF without the patient cable connected to the testing circuit. The shield of the patient cable must not be connected.

Noise level

With the ECG set to the widest bandwidth for the resting ECG application, the line frequency notch filter if any, set to the appropriate mains frequency, and all other switchable filters switched off, the noise level shall not exceed 30 μV peak-to-valley referred to the input over a period of 10 seconds. This shall be done using the patient cable specified by the manufacturer and with all lead electrodes connected to a

common junction with 51 kΩ resistor and parallel to 47 nF capacitor and in series together with the lead wires.

Use the manufacturer specified patient cable(s) for the following test:

a) Insert in series a 51 kΩ resistor with each lead wire of the patient cable and then parallel with a 47 nF capacitor as shown in testing circuit of Figure 46 (Note for this test all the switches S1 through Sn are open, S_{DC} is in position B, and the 20 V source from signal generator and the 100 pF capacitor are not connected (S0 open).

b) With the ECG set to its highest gain setting and widest bandwidth setting, and with the filters set, check that the noise on the ECG report does not go beyond 30 μV peak-to-valley referred to input for a period of at least 10 seconds, in each position of the selector lead switch.

This test will be repeated for nine times. Ensure that the 30 μV limit do not exceeded for a minimum nine out of 10 trials. The 10 trials shall occur within 30 minutes or less. The patient cable and its connector shall be motionless during these tests. The patient cable shall not be disconnected between trials.

Step 3: Requires the involvement of notified body due to class/ category

The ABI device has two functions where it records the electrical signal of the ECG and light intensity of the PPG. With reference to Part III (Classification) in Annex IX (Classification criteria), the most applicable path for the device to follow will be the path for active devices. Under the active devices path of Annex IX, the suitable

classification of the device will be to follow Rule 10 as stated that the intended use is to acquire the readings of the vital physiological parameters during routine checkups. Therefore, according to Rule 10 of Annex IX, the device can be classified as a Class IIa device of medium risk under the MDD. Figure 47 shows the classification path of the ABI device.

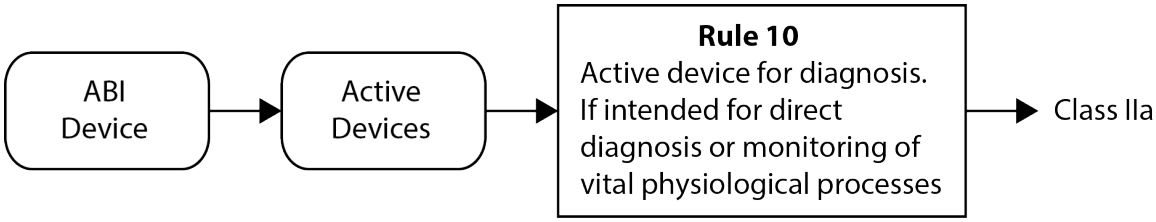


Figure 47 - Classification path of ABI Device (Rule 10)

With the selected directive to be MDD in Step 1, the available notified bodies can be found from the database of NANDO or in Appendix A3. Assuming that the chosen notified body to be SGS United Kingdom Limited (NB 0120) from United Kingdom, SGS UK Ltd will be responsible for the inspection of the chosen conformity assessment option in Step 4.

Step 4: Selection of conformity assessment route and declaration of conformity

The ABI device has been classified as a Class IIa device according to Step 3. With reference to Article 11 paragraph 2 of MDD, there are four possible routes which the researcher can choose from:

1) Route 1: according to Annex II (Full quality)

2) Route 2: according to Annex VII in combination with Annex IV(Verification)
3) Route 3: according to Annex VII in combination with Annex V (Production)
4) Route 4: according to Annex VII in combination with Annex VI (Product)

Route 1 is not looked into as it is the easiest but costly route for researchers with limited budget to commercialize their product. Route 2 has Annex IV that deals with statistical verification of products and is recommended for products manufactured in mass production so it is not a suitable route for the ABI device. Route 3 has Annex V that deals with the inspection and quality of the manufacturing stages which in particular regards to the sterilization of the product. Route 4 has Annex VI that deals with the examination of every product or a representative sample from each batch. Comparing Route 3 with Route 4, the procedure according to Route 4 is more relevant to be conducted for the ABI device as the manufactured device have tested for the performance of the functions available for capturing the readings. Thus the route according to Annex VII in combination with Annex VI is suitable for the ABI device of Class IIa. Figure 48 shows the chosen conformity route for the ABI device.

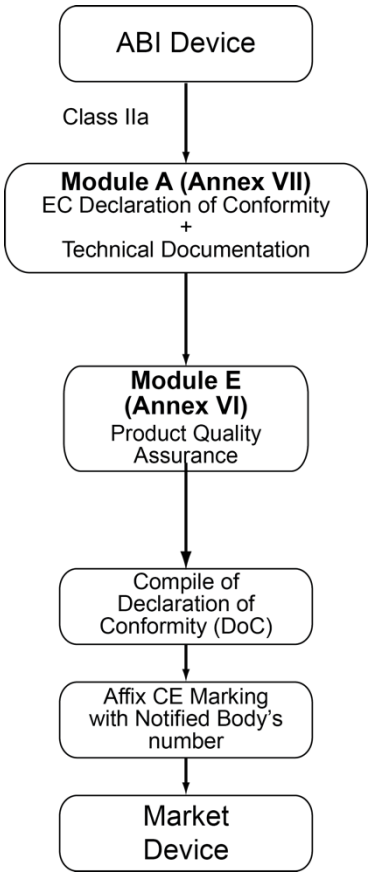


Figure 48 - Conformity Route (Annex VII & Annex VI) for ABI Device

The assessment of the conformity route, Annex VI, will be inspected by the chosen notified body, SGS United Kingdom Limited, in Step 3. During the inspection of the conformity route, the researcher can start to compile and do up the conformity declaration document with the necessary information. The requirement of an authorized representative (EC Rep) is needed for the device to be sold in Europe and the selected EC Rep is Emergo Europe. Figure 49 show a mock version with necessary details of the DoC that needs to be drawn up for the ABI device.

NGEE ANN POLYTECHNIC	**DECLARATION OF CONFORMITY**

Manufacturer:
NP Enterprise (S) Pte Ltd
c/o Ngee Ann Polytechnic
535 Clementi Road
Singapore 599489
Tel: +65 6460 6059

Notified Body:
SGS United Kingdom Limited
Unit 202B, Worle Parkway, Weston-super-Mare,
North Somerset, BS22 6WA, United Kingdom
Tel: +44 (0) 1934 522917
Fax: +44 (0) 1934 522137

European Representative:
Emergo Europe
Molenstraat 15, 2513 BH, The Hague
The Netherlands
Tel: +31 (0) 70 345 8570
Fax: +31 (0) 70 346 7299

Medical Device(s):

1. Ankle Brachial Index (ABI) Device

We herewith declare that the above-mentioned product meets the provisions of the Council Directive 93/42/EEC (MDD). All supporting documentation is retained under the premises of the manufacturer.

Device Classification: Class IIa (Rule 10), non-invasive, active device

Standards Applied:
EN 60601-1:2006
EN 60601-2-27:2014
EN ISO 80601-2-61:2011

Decision according to Annex VII and Annex VI (product quality assurance) of Council Directive 93/42/EEC concerning medical devices.

Place: NP Enterprise (S) Pte Ltd, Singapore

Date: November 12, 2015

Signature:

Name: XX XXX XXXX
Director of NP Enterprise (S) Pte Ltd

Figure 49 - Declaration of Conformity for ABI Device

Step 5: Do up and maintain the availability of technical documents

The technical document will have to include the DoC of Figure 49, risk analysis report referencing to ISO 14971, clinical trial data, mechanical and electrical construction data including drawings and explanation, etc. Given that the device is being developed out of the European Union countries (in Singapore), the appointed authorized representative (Emergo Europe) has to keep a duplicated copy of the actual technical documents provided by the manufacturer with a duration of no less than 5 years when the device is available in the EU market.

Step 6: Attach and placement of CE marking

After the compilation of the technical document is done in Step 5, only then can the CE marking be affixed onto the device and be marketed as a medical device in the European community. The ABI device does have visible space on the back of the casing to place the CE marking and also on the packaging and the accompany document like the instruction of use. It is stated clearly in Step 3 that there is an involvement of notified body, SGS United Kingdom Limited, in performing the conformity assessment options (Annex VII and Annex VI) stated in Step 4, therefore the identification number CE0120 is needed to be displayed on the device casing, packaging and accompany document.

5.5 Summary

With the application of the CE medical decision model on the three research devices, it shows possibility in the usefulness of the decision model. The first device, Wheelchair Gap Enabler, was tested on the CE medical decision model and had a smooth flow and clarity in the selection of the choices. Figure 50 shows an overview of the finalized CE medical decision model for the Wheelchair Gap Enabler where all the steps are being addressed. From the first case study, it can be observed that the CE decision model is able to handle a Class I device in fulfilling the regulatory requirements before embarking on the path in getting it commercialized in EU.

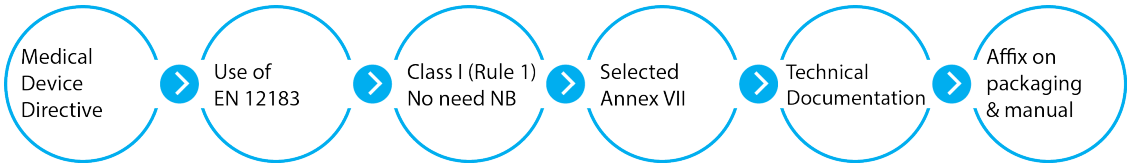


Figure 50 - CE Medical Decision Model applied on Wheelchair Gap Enabler

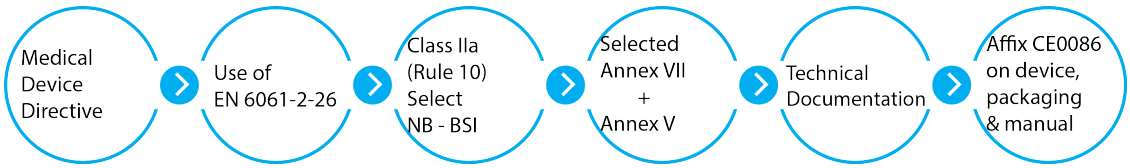


Figure 51 - CE Medical Decision Model applied on SynPhNe System

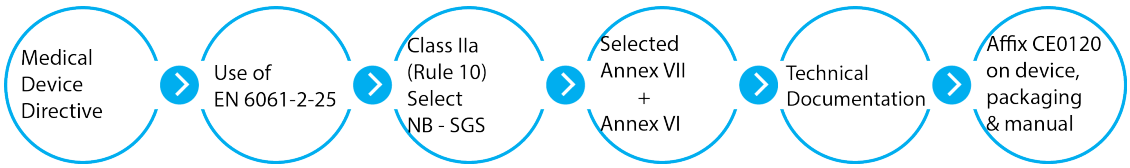


Figure 52 - CE Medical Decision Model applied on ABI Device

The second device, SynPhNe system, was tested with the CE medical decision model and was able to get its device classification of Class IIa easily with the applicable directive, definition and rules guidance. Figure 51 shows an overview of the finalized CE medical decision model for the SynPhNe System.

The third and last device, ABI device, was tested with the CE medical decision model and again was able to get its classification of Class IIa without any hesitant in the decision process. Figure 52 shows an overview of the finalized CE medical decision model for the ABI device. Figure 51 and 52 does show a similarity in the selected directive and classification even though one of them is a system while the other is a device. But it is clear that the standard applied was for different purposes and the conformity assessment options selected was to inspect on different aspects of the product related.

The decision model does show that it is able to get either an accessory, a system or a device into the appropriate classification and also helping in the choice selection of each step. Lastly in this chapter, some assumptions were made to help in understanding the flow of the CE medical decision model such as the selection of the notified bodies for the Class IIa devices and also the selection of authorized representative.

CHAPTER SIX

CONCLUSION

6.1 Discussion

It is common that most device researchers may still be unaware of the need to classify or choose a directive for their developed device until they intend to bring their device to commercialization. Researchers who have secured public-funded research grants, need to be prudent as there is an increasing need for them to commercialize the end product of their research in a sizable market such as the EU. In this thesis, the few companies in Chapter 2 were listed out to show the vast differences and possible confusions between the various steps used in the CE marking regulatory processes. With that many options available, it can be difficult and tedious process for the researcher to start searching for regulatory information to aid them in the commercialization path. It is also noted that the regulatory process for approving medical devices is lengthy and it will also incur high expenses on the limited funding that the researchers have.

While the ultimate goal for every researcher, awarded with the research grant, is to improve the quality of life of patients but the cruel reality will eventually set in if the regulatory requirements are not deal with during the development phase. Only approved medical devices can benefit patients directly as these can then be marketed to healthcare institutions as a regulated device. With the necessity of including the regulatory requirements in the development phase, Chapter 4 focuses on forming the CE medical decision model in order to assist the researchers in deciding the appropriate

choice that the device eventually will be conforming upon the route to commercialization.

The CE medical decision model was then applied on three research devices and shows a generally clear structure in obtaining the CE marking for the different medical devices. Therefore, it is worth highlighting the importance to all researchers on understanding the regulatory requirements for CE marking and applying the CE medical decision model concurrently with the development work in order to develop and prepare for commercialization of the medical devices at a faster pace.

6.2 Conclusion

This thesis covers the necessary regulatory requirements that a device researcher needs to consider when the device is being developed. While this knowledge may be well understood by seasoned medical grade device manufacturers, many researchers may not be aware of such regulatory requirements especially for a sizable and well regulated market like the EU. With the use of the CE medical decision model, it helps the researcher in choosing an appropriate regulatory choice that will eventually help in bringing the developed device out to the market at a much faster pace. Therefore, researchers must have the regulatory requirements in mind before they embark on the device development or they will face the risks of their device not adequately meeting the regulatory requirements and thereby delaying their period of commercialization and subsequently not benefiting the original intended beneficiaries in improving their quality of life.

6.3 Future works

With this designed CE medical decision model serving as the starting point for researchers to have a better understanding in the regulatory requirements, further research works or studies can be done to help enhance the robustness of the decision model.

The first possible work can be to further developed the CE medical decision model into an online version available to assist researchers by showing each step at a time the possible choices to choose from and subsequently listing the chosen path.

The second possible work to looked into can be on the application of the QMS, as mention with a brief introductory in Chapter 3. The QMS was not covered in the CE medical decision model and this area can be crucial when the conformity assessment procedure on the assurance of the quality is involved. The application of QMS will further look into the management team structure, the process on the development of the product, etc. With the focus on applying the QMS on real medical device cases, it can help researchers to organized their team structure and plan out their task responsibilities efficiently even before the commencement of the design and development of the product.

The third possible work that can be focus on is the application of the risk management which was briefly introduced in Chapter 3 for researchers to under the importance but was not included in the CE medical decision model. This area is also deemed crucial to for researchers to be able to minimize or even better to eliminate the risk of the

developed device that might harm the end users. With a study to be done on the risk management, it can further enhance the CE medical decision model in the conformity assessment route where the risk is one of the crucial factor in deciding on the possibility of the device being able to enter the market with safety assurance for the final users.

With these three areas to focus on, it will definitely assist any researcher in fulfilling the regulatory requirements and thus developing a better compliance medical device in a much shorter time for commercialization to commence.

REFERENCES

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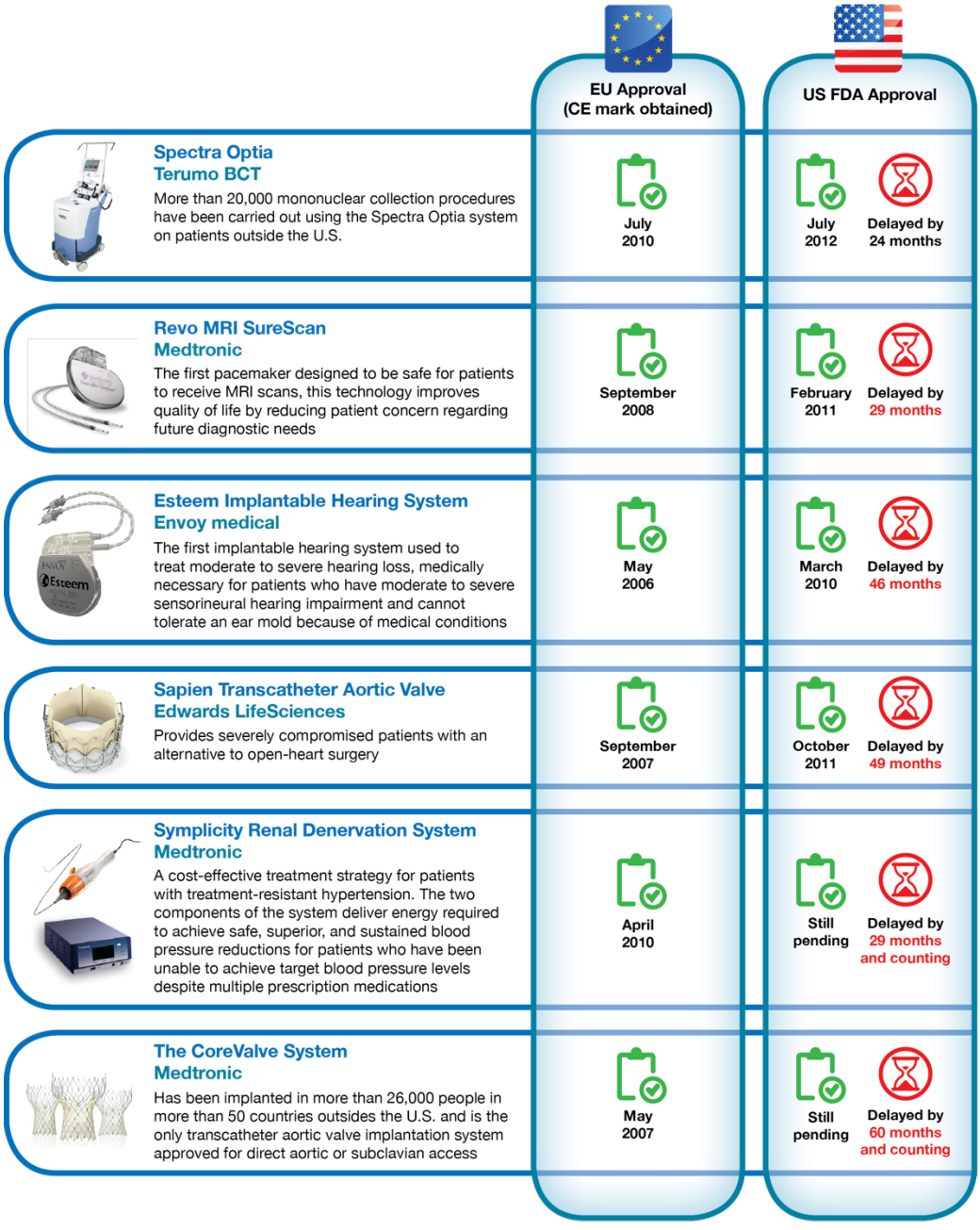
APPENDICES

APPENDIX A1

Patient Access to Medical Technology in the EU and US



Sources: Boston Consulting Group, 2012; and other public sources

Eucomed Medical Technology
www.eucomed.org

APPENDIX A2

List of Member States Competent Authorities for Medical Devices

Country	Competent Authority
Austria	Federal Ministry of Health, Dept. Pharmaceuticals and Medical Devices
Belgium	a. Federal Agency for Medicines and Health Products Health Products Division (MDD, AIMDD) b. Scientific Institute Public Health, Department Quality Medical Laboratories (IVDMD)
Bulgaria	Bulgarian Drug Agency Department Medical devices
Croatia	Agency for Medicinal products and medical devices
Cyprus	Cyprus Medical Devices Competent Authority
Czech Republic	Ministry of Health Department of Pharmacy, Medical Devices Unit
Denmark	Danish Health and Medicines Authority, Pharmacovigilance and Medical Devices
Estonia	Health Board, Medical Devices Department
Finland	Valvira - National Supervisory Authority for Welfare and Health
France	Agence nationale de sécurité du médicament et des produits de santé (ANSM)
Germany	a. Federal Ministry of Health (AIMDD, MDD, IVDMD Legislation) b. Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG) (AIMDD, MDD, IVDMD Designating) c. Federal Institute for Drugs and Medical Devices d. Paul Ehrlich Institute, Section Pharmacovigilance 2 (IVDMD)
Greece	National Organization for Medicines

Hungary	Health Registration and Training Centre, Department of Medical Devices
Iceland (ETFA)	Icelandic Medicines Agency
Ireland	Health Products Regulatory Authority
Italy	Ministry of Health, Department of Planning and Organisation of the National Health Service - Directorate General of Medical Devices, pharmaceutical services and safety in healthcare
Latvia	State Agency of Medicines
Liechtenstein	Amt für Gesundheit
Lithuania	The State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania
Luxembourg	Ministère de la Santé, Direction de la Santé
Malta	Malta Competition and Consumer Affairs Authority
Netherlands	a. Notification/Registration CIBG Farmatec-BMC, Front Office b. Law Enforcement (a.o. vigilance and market surveillance) Dutch Healthcare Inspectorate, IGZ information office (Meldpunt)
Norway (EFTA)	Helsedirektoratet / Norwegian Directorate for Health
Poland	a. Office for Registration of Medicinal Products, Medical Devices and Biocidal Products b. Ministry of Health
Portugal	Infarmed - National Authority of Medicines and Health Products, IP
Romania	National Agency for Medicines and Medical Devices
Slovakia	State Institute for Drug Control, Medical Devices Section
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Spain	Agencia Espaňola de Medicamentos y Productos Sanitarios

Sweden	Medical Products Agency´ 'Läkemedelsverket' Medical Devices
Switzerland (EFTA)	Swissmedic, Swiss Agency for Therapeutic Products
Turkey (Candidate)	Ministry of Health , DG for Pharmaceuticals and Pharmacy, Department of Medical Device Services, Market Surveillance Section
United Kingdom	Medicines & Healthcare products Regulatory Agency (MHRA)

APPENDIX A3

List of Notified Bodies for Medical Device Directives

Active Implantable Medical Device Directive (90/385/EEC)

S/No	Body Type	Name	Country	End of Validity Date
1	NB 0636	PRÜFSTELLE FÜR MEDIZINPRODUKTE GRAZ	Austria	Unlimited
2	NB 1014	ELEKTROTECHNICKÝ ZKUŠEBNÍ ÚSTAV, s.p.	Czech Republic	Unlimited
3	NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s.	Czech Republic	Unlimited
4	NB 0459	Laboratoire national d'essais / G-MED	France	Unlimited
5	NB 0044	TÜV NORD CERT GmbH	Germany	31/12/2099
6	NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany	Unlimited
7	NB 0197	TÜV Rheinland LGA Products GmbH	Germany	31/12/2099
8	NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany	Unlimited
9	NB 0535	BSI Group Deutschland GmbH	Germany	Unlimited
10	NB 1275	LGA INTERCERT ZERTIFIZIERUNGSGESELLSCHAFT MBH	Germany	31/12/2099

11	NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary	17/09/2015
12	NB 0050	National Standards Authority of Ireland (NSAI)	Ireland	Unlimited
13	NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy	Unlimited
14	NB 0344	DEKRA Certification B.V.	Netherlands	24/09/2016
15	NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland	14/10/2016
16	NB 0318	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS	Spain	31/12/2020
17	NB 0086	BSI	United Kingdom	Unlimited

Medical Device Directive (93/42/EEC)

S/No	Body Type	Name	Country	End of Validity Date
1	NB 0408	TÜV AUSTRIA SERVICES GMBH	Austria	31/12/2018
2	NB 0636	PRÜFSTELLE FÜR MEDIZINPRODUKTE GRAZ	Austria	Unlimited
3	NB 0029	APRAGAZ A.S.B.L.	Belgium	03/06/2015
4	NB 1639	SGS Belgium NV	Belgium	09/05/2016
5	NB 1014	ELEKTROTECHNICKÝ ZKUŠEBNÍ ÚSTAV, s.p.	Czech Republic	Unlimited
6	NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s.	Czech Republic	Unlimited
7	NB 2291	Chemila, spol. s r. o.	Czech Republic	Unlimited
8	NB 0543	Presafe Denmark A/S	Denmark	Unlimited
9	NB 0537	VTT Expert Services Oy	Finland	30/10/2018
10	NB 0598	SGS FIMKO OY	Finland	30/05/2016
11	NB 0459	Laboratoire national d'essais / G-MED	France	Unlimited
12	NB 0044	TÜV NORD CERT GmbH	Germany	Unlimited
13	NB	TÜV SÜD Product Service GmbH	Germany	Unlimited

	0123	Zertifizierstellen		
14	NB 0124	DEKRA Certification GmbH	Germany	31/12/2099
15	NB 0197	TÜV Rheinland LGA Products GmbH	Germany	31/12/2099
16	NB 0297	DQS Medizinprodukte GmbH	Germany	31/12/2099
17	NB 0366	VDE - Prüf- und Zertifizierungsinstitut GmbH	Germany	Unlimited
18	NB 0432	Materialprüfungsamt Nordrhein-Westfalen (MPA NRW)	Germany	31/12/2099
19	NB 0481	ECM-ZERTIFIZIERUNGSGESELLSCHAFT FÜR MEDIZINPRODUKTE IN EUROPA MBH	Germany	Unlimited
20	NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany	31/12/2099
21	NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany	Unlimited
22	NB 0494	SLG PRÜF UND ZERTIFIZIERUNGS GMBH	Germany	Unlimited
23	NB 0535	BSI Group Deutschland GmbH	Germany	Unlimited
24	NB 0633	BERLIN CERT PRÜF- UND ZERTIFIZIERSTELLE FÜR MEDIZINPRODUKTE GMBH AN DER TECHNISCHEN UNIVERSITÄT BERLIN	Germany	Unlimited

25	NB 1275	LGA INTERCERT ZERTIFIZIERUNGSGESELLSCHAFT MBH	Germany	31/12/2099
26	NB 0653	NATIONAL EVALUATION CENTER OF QUALITY AND TECHNOLOGY IN HEALTH S.A.- EKAPTY	Greece	Unlimited
27	NB 1008	TÜV Rheinland InterCert Muszaki Felügyeleti és Tanúsító Korlátolt Felelosségu Társaság	Hungary	Unlimited
28	NB 1011	Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet Eszközminősítő és Kórháztechnikai Igazgatóság (National Institute for Quality- and Organizational Development in Healthcare and Medicines Directorate of Device Testing and Engineering)	Hungary	30/04/2015
29	NB 1979	SGS Hungária Minoségellenorzo, Kereskedelmi és Szolgáltató Kft.	Hungary	Unlimited
30	NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary	17/09/2015
31	NB 0050	National Standards Authority of Ireland (NSAI)	Ireland	Unlimited
32	NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy	10/05/2017
33	NB 0068	IRCM ISTITUTO DI RICERCHE E COLLAUDI MASINI S.R.L.	Italy	06/01/2018
34	NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy	Unlimited

35	NB 0398	APAVE ITALIA CPM SRL	Italy	Unlimited
36	NB 0425	ICIM S.P.A.	Italy	16/02/2016
37	NB 0426	ITALCERT SRL	Italy	14/02/2017
38	NB 0476	KIWA CERMET ITALIA S.P.A.	Italy	11/02/2018
39	NB 0477	Eurofins TECH S.r.l.	Italy	16/04/2018
40	NB 0546	CERTIQUALITY S.R.L. - ISTITUTO DI CERTIFICAZIONE DELLA QUALITA'	Italy	26/03/2017
41	NB 1370	BUREAU VERITAS ITALIA S.P.A.	Italy	26/09/2018
42	NB 1936	TUV Rheinland Italia SRL	Italy	08/01/2018
43	NB 0499	SOCIETE NATIONALE DE CERTIFICATION ET D'HOMOLOGATION S.À.R.L. (SNCH)	Luxembourg	Unlimited
44	NB 0344	DEKRA Certification B.V.	Netherlands	24/09/2016
45	NB 0434	DNV GL Business Assurance Norway AS	Norway	Unlimited
46	NB 0470	NEMKO AS	Norway	Unlimited
47	NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland	14/10/2016
48	NB	Oficiul Tehnic de Dispozitive Medicale	Romania	Unlimited

	1868	Certificare-OTDM CERTIFICARE		
49	NB 1293	EVPU a.s.	Slovakia	Unlimited
50	NB 1297	VYSKUMNY USTAV ZVARACSKY - PRIEMYSELNY INSTITUT SLOVENSKEJ REPUBLIKY	Slovakia	17/03/2015
51	NB 2265	3EC International a.s.	Slovakia	01/09/2016
52	NB 1304	SLOVENIAN INSTITUTE OF QUALITY AND METROLOGY - SIQ	Slovenia	09/03/2015
53	NB 0318	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS	Spain	15/12/2020
54	NB 0402	SP Sveriges Tekniska Forskningsinstitut AB/ SP Technical Research Institute of Sweden	Sweden	Unlimited
55	NB 0413	INTERTEK SEMKO AB	Sweden	Unlimited
56	NB 1783	TURKISH STANDARDS INSTITUTION (TSE)	Turkey	Unlimited
57	NB 1984	Kiwa Meyer Belgelendirme Hizmetleri A.Ş.	Turkey	31/12/2099
58	NB 2138	Alberk QA Uluslararası Teknik Kontrol ve Belgelendirme Anonim Şirketi	Turkey	13/01/2015
59	NB 2195	Szutest Teknik Kontrol ve Belgelendirme Hizmetleri Ticaret Limited Şirketi	Turkey	24/11/2017
60	NB 2292	UDEM Uluslararasi Belgelendirme Denetim Egitim Merkezi Sanayi ve Ticaret Limited Sirketi	Turkey	13/01/2015

61	NB 0086	BSI	United Kingdom	Unlimited
62	NB 0088	LLOYD'S REGISTER QUALITY ASSURANCE LTD (0088)	United Kingdom	Unlimited
63	NB 0120	SGS United Kingdom Limited	United Kingdom	Unlimited
64	NB 0473	AMTAC CERTIFICATION SERVICES LTD	United Kingdom	Unlimited
65	NB 0843	UL INTERNATIONAL (UK) LTD	United Kingdom	Unlimited
66	NB 0805	THERAPEUTIC GOODS ADMINISTRATION	Australia (MRA)	Unlimited
67	NB 1250	SCHWEIZERISCHE VEREINIGUNG FÜR QUALITÄTS- UND MANAGEMENTSYSTEME	Switzerland (MRA)	Unlimited
68	NB 1253	Swiss TS Technical Services AG	Switzerland (MRA)	Unlimited
69	NB 1254	QS Zürich AG	Switzerland (MRA)	Unlimited

***In vitro* Diagnostic Medical Device Directive (98/79/EC)**

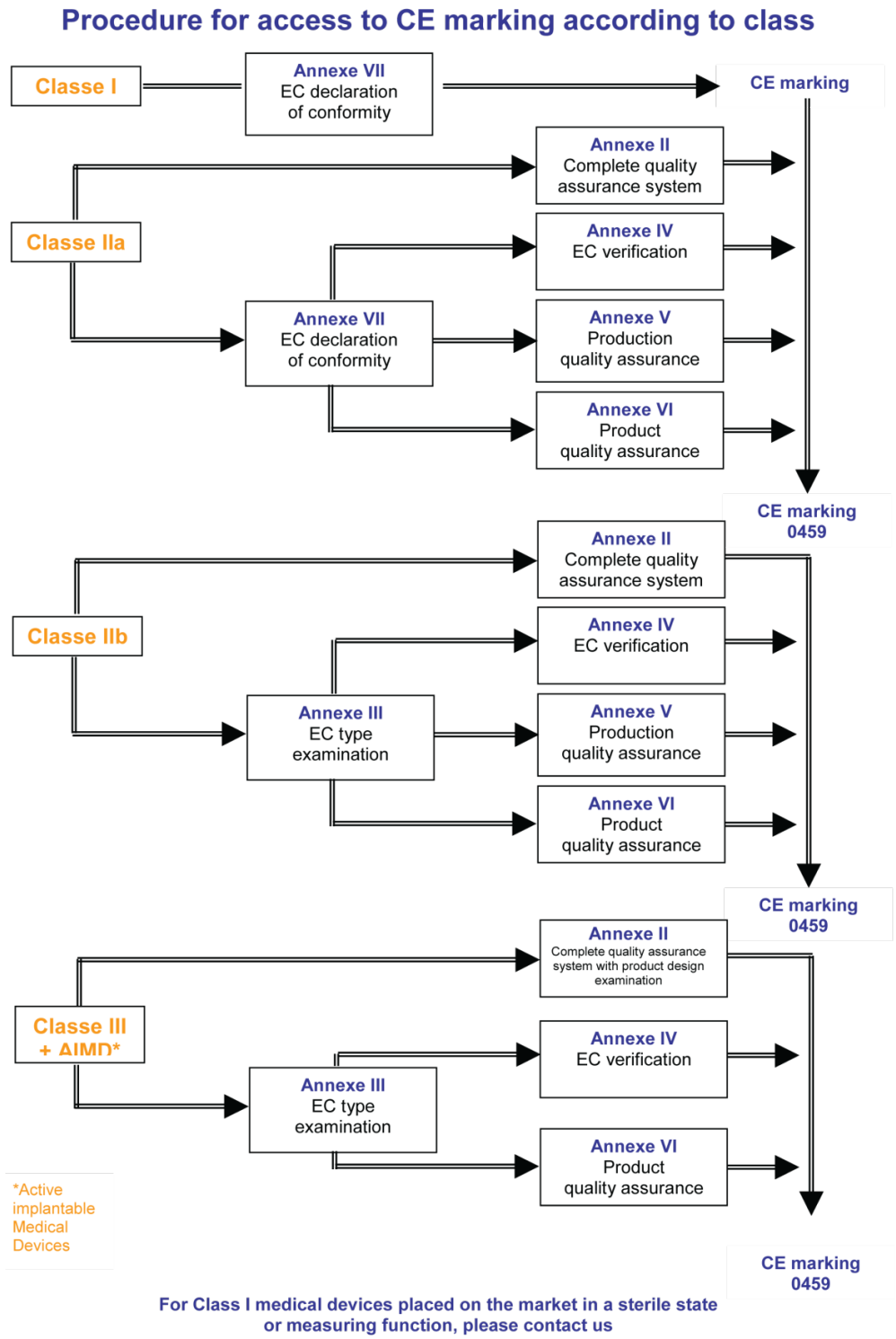
S/No	Body Type	Name	Country	End of Validity Date
1	NB 0408	TÜV AUSTRIA SERVICES GMBH	Austria	31/12/2018
2	NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s.	Czech Republic	Unlimited
3	NB 0543	Presafe Denmark A/S	Denmark	Unlimited
4	NB 0537	VTT Expert Services Oy	Finland	31/12/2090
5	NB 0459	Laboratoire national d'essais / G-MED	France	Unlimited
6	NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany	Unlimited
7	NB 0124	DEKRA Certification GmbH	Germany	31/12/2099
8	NB 0197	TÜV Rheinland LGA Products GmbH	Germany	31/12/2099
9	NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany	Unlimited
10	NB 0535	BSI Group Deutschland GmbH	Germany	Unlimited
11	NB 1011	Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet Eszközminősítő és Kórháztechnikai Igazgatóság (National Institute for Quality- and	Hungary	26/07/2016

		Organizational Development in Healthcare and Medicines Directorate of Device Testing and Engineering)		
12	NB 1979	SGS Hungária Minoségellenorzo, Kereskedelmi és Szolgáltató Kft.	Hungary	Unlimited
13	NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary	17/09/2015
	Nil	Nil	Iceland	Nil
14	NB 0050	National Standards Authority of Ireland (NSAI)	Ireland	Unlimited
15	NB 0344	DEKRA Certification B.V.	Netherlands	24/09/2016
16	NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland	14/10/2016
17	NB 1293	EVPU a.s.	Slovakia	Unlimited
18	NB 2265	3EC International a.s.	Slovakia	01/09/2016
19	NB 0318	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS	Spain	31/12/2020
20	NB 1783	TURKISH STANDARDS INSTITUTION (TSE)	Turkey	Unlimited
21	NB 0086	BSI	United Kingdom	Unlimited
22	NB 0088	LLOYD'S REGISTER QUALITY ASSURANCE LTD (0088)	United Kingdom	Unlimited
23	NB	SGS United Kingdom Limited	United	Unlimited

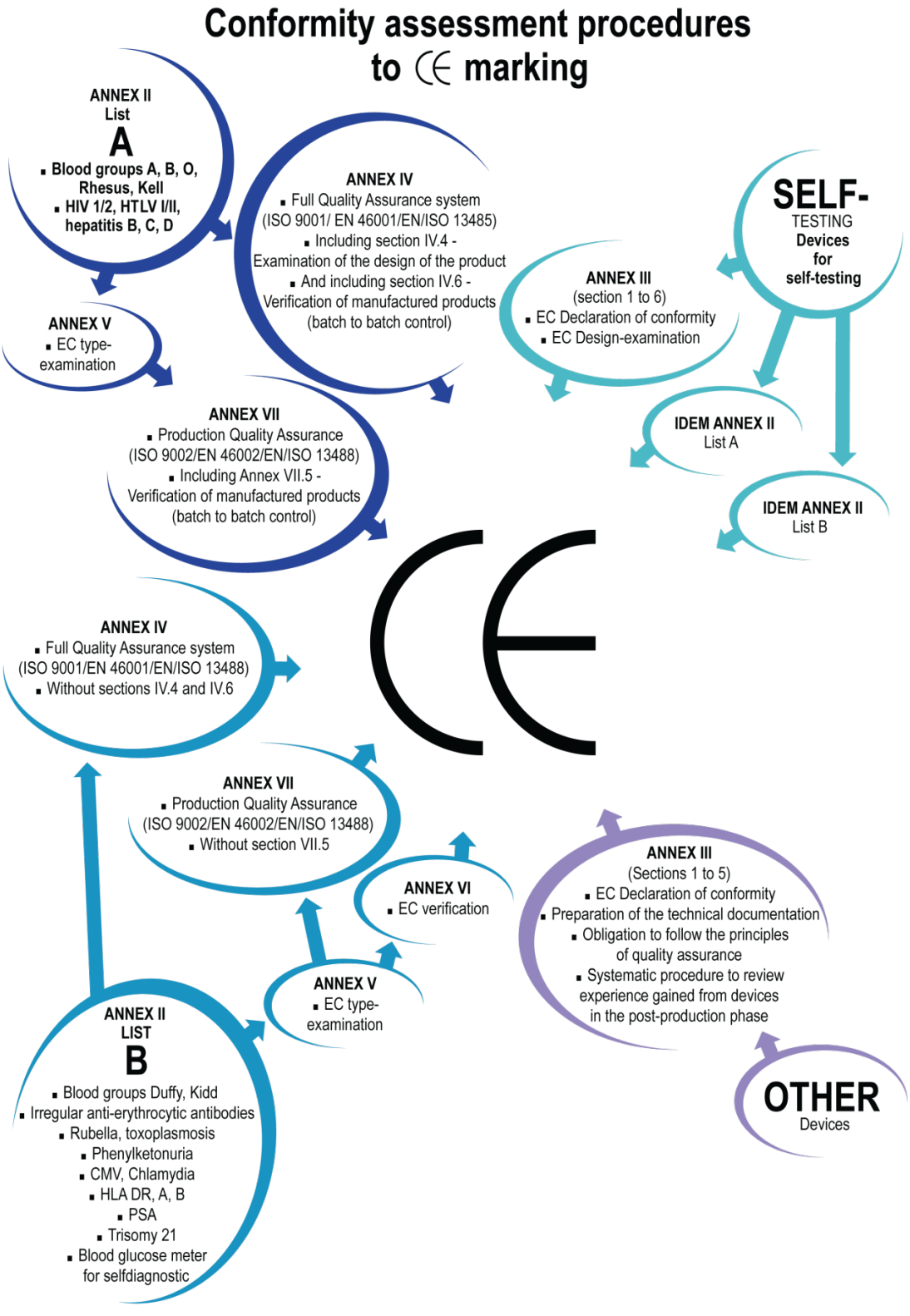
	0120		Kingdom	
24	NB	UL INTERNATIONAL (UK) LTD	United	Unlimited
	0843		Kingdom	
25	NB	SCHWEIZERISCHE	Switzerland	Unlimited
	1250	VEREINIGUNG FÜR QUALITÄTS-	(MRA)	
		UND MANAGEMENTSYSTEME		

APPENDIX B1

LNE/GMED: AIMDs and MDs procedure for access to CE Marking



LNE/GMED: IVDMDs conformity assessment procedures



SGS

CE MARKING PROCESS

1. Identify the **Directive(s)** that are applicable

2. Choose the **conformity assessment procedure**
3. Identify any **Harmonised European Standards** applicable (not mandatory , presumption of conformity)
4. Is Notified Body required ? Ask a proposal for certification.

5. Ensure to comply with all the **essential requirements**
6. Maintain **Technical Documentation**

7. Certification of the QMS and review of the Technical Documentation by the Notified Body (if applicable)
8. **Declaration of Conformity** and the supporting evidence.

9. Check that no other purely **national** requirements exist
10. Affix **CE marking** on your product

APPENDIX B3

TÜV Rheinland Group: Proven Steps on the Way to CE Marking

Manufacturers must comply with the medical device directives in order to sell into the European marketplace. TUV Rheinland of North America with the Notified Bodies can help you carry out your conformity assessment procedure for CE Marking as well as assist you to acquire worldwide approval of your medical devices. TÜV offers a comprehensive range of services.

Steps to acquiring the CE marking include:

1. **Definition of the medical device and intended use**
   As a manufacturer, you determine the intended use of your device. This results in a decision as to which directive is applicable to your medical device (MDD, AIMD or IVDD).

2. **Classification of the medical device**
   In the MDD, medical devices are classified in accordance with the regulations in Annex IX. The AIMD does not provide for any classification. The IVDD distinguishes between products for self-testing, for performance evaluation, Lists A and B and products which do not fall into any of the categories named.

3. **Determination of the suitable procedure for conformity assessment**
   Depending on the classification of the product, a "Notified Body" is required, which, for example, you will entrust with carrying out an EC type examination, with assessing a design dossier and/or with auditing your QM system. AIMD products always require the involvement of a "Notified Body".

4. **Technical documentation**
   The manufacturer must prepare technical documentation for every type of medical device, which essentially consists of the following: description of the device, design documents, the standards applied and a description of the solutions chosen to meet the essential requirements, risk analysis, test reports, clinical evaluation, labeling and instructions for use, and additionally for sterile device descriptions of the sterilization procedures used and the validation certificates.

Medical devices must fulfill the applicable essential requirements listed in Annex I of the respective directive.

Proof must be provided that the safety requirements have been met and that the technical services have been rendered. An assessment procedure also must be provided. The medical effectiveness must be proven through a clinical assessment. The manufacturer is free to choose how he will provide proof that the essential requirements have been met.

As a test body for medical devices, TÜV Rheinland can conduct necessary tests, such as safety, functional and biocompatibility tests, which can then be used as acknowledged proof for your technical documentation.

5. EC type examination or examination of the design of the product

For all AIMD, MDD Class III and IVDD List A products, the manufacturer must decide between the EC type examination procedure and the examination of the product design documentation (design dossier). In this process, TUV Rheinland of North America with the Notified Body can test either the product or the design dossier. After successful examination, the certification body of TÜV Rheinland issues an approval in accordance with the directive.

6. Implementation of the conformity assessment procedure

Manufacturers of medical devices generally choose to audit their quality management systems. The auditors assess the documentation of the QM system prior to the audit and verify the application of the written procedures during the audit at the company location. The duration of the audit and the number of auditors required will depend on the size of the company and the number of different products covered. This information (size and number of products) is provided to TÜV Rheinland in each company's individual quotation. After the audit, you will receive a written report with the audit results.

As an alternative to the audit, a manufacturer can choose the EC verification procedure (sampling or individual testing) in accordance with Annex IV (MDD) or Annex VI (IVDD). Upon successful completion of the conformity assessment procedure, the Notified Body will issue an approval for the CE Marking of your devices.

APPENDIX B4

MDC GmbH: Steps in Certification Procedure of MDD 93/42/EEC

medical device certification mdc	**Basic Information MDD 93/42/EEC**

HOW TO OBTAIN THE CE-MARK – STEPS IN THE CERTIFICATION PROCEDURE

I. GENERAL

As mentioned in previous chapters the European Medical Devices Directives focus on the responsibility of the device manufacturers. Therefore CE marking for all medical devices requires among others a technical documentation, a risk analysis, a proof of compliance with the essential requirements of the directive and a product-related declaration of conformity issued by the manufacturer.

Only non-sterile class I devices without measuring function do not require the involvement of a Notified Body. The manufacturer of such devices marks them under his sole responsibility with the CE-mark without a number.

All other devices require the certification by a Notified Body before the manufacturer can put the CE-mark in combination with the number of the Notified Body on the device. Depending on the device class the manufacturer has the choice between different certification routes as graphically shown on the following pages.

The certification usually includes the following steps:

- decision whether or not a product is a medical device and by which of the European Medical Devices Directives it is covered
- classification of the device(s) by the manufacturer
- contact to Notified Bodies, preliminary discussions and exchange of information, choice of the Notified Body
- answering of specific questions of the chosen Notified Body (usually by filling out a questionnaire provided by the Notified Body); confirmation of device classification by the Notified Body, time and cost estimation for different certification routes; choice of the certification route by the manufacturer
- formal application and certification contract
- submission of documents to the Notified Body
- evaluation of the submitted documents and report
- audit of the manufacturer's operations and if applicable and required also suppliers' and/or subcontractors' facilities including reporting
- decision about the certification and issuing of the relevant certificate(s), which are usually valid for five years
- surveillance audits (performed by mdc annually)
- full re-audit and issuing of a new certificate usually after five years

The following pages contain diagrams with the various certification routes and a brief description of Annexes II - VII of the MDD.

MDC GmbH: Steps in Certification Procedure of IVDMDD 98/79/EC

medical device certification mdc ein Unternehmen von ZDH-ZERT	**Basic Information IVDD 98/79/EC**

How to Obtain the CE-Mark – Steps in the Certification Procedure

I. General

As mentioned in previous chapters the European Medical Devices Directives focus on the responsibility of the device manufacturers. Therefore CE marking for all medical devices requires among others a technical documentation, a risk analysis, a proof of compliance with the essential requirements of the directive and a product-related declaration of conformity issued by the manufacturer.

IVD manufacturers, who have no devices listed in Annex II, no devices for self-testing and no devices for performance evaluation, do not require the involvement of a Notified Body. The manufacturer of such devices marks them under his sole responsibility with the CE mark without a number.

Devices according to Annex II and devices for self-testing require the certification by a Notified Body before the manufacturer can put the CE mark in combination with the number of the Notified Body on the device. Depending on the listing of the in vitro diagnostic device, the manufacturer has the choice between different certification routes as graphically shown on the following pages.

The certification usually includes the following steps:

- decision whether or not a product is an in-vitro diagnostic medical device in the sense of the IVDD
- categorization of the device(s) by the manufacturer
- contact to Notified Bodies, preliminary discussions and exchange of information, choice of the Notified Body
- answering of specific questions of the chosen Notified Body (usually by filling out a questionnaire provided by the Notified Body); confirmation of device categorization by the Notified Body, time and cost estimation for different certification routes; discussion and choice of the most suitable certification route by the manufacturer
- formal application and certification contract
- submission of documents to the Notified Body
- evaluation of the submitted documents and report
- if required performance of product testing
- audit of the manufacturer's operations and if applicable and required also suppliers' and/or subcontractors' facilities including reporting
- decision about the certification and issuing of the relevant certificate(s), which are usually valid for five years
- in case of Annex II list A devices evaluation of the manufactured device batches by the Notified Body
- surveillance audits (usually one audit per year)
- full re-audit and issuing of a new certificate after five years

The following pages contain diagrams with the various certification routes and a brief description of Annexes III - VII of the IVDD.

APPENDIX B5

BSI: The Route to CE Marking

THE ROUTE TO CE MARKING

CE marking is a legal requirement for devices intended for sale in Europe. The route to achieving CE Marking can seem complex and confusing, but when you partner with a well versed Notified Body, like BSI, this process will move smoothly and efficiently.

The key stages of CE Marking are:

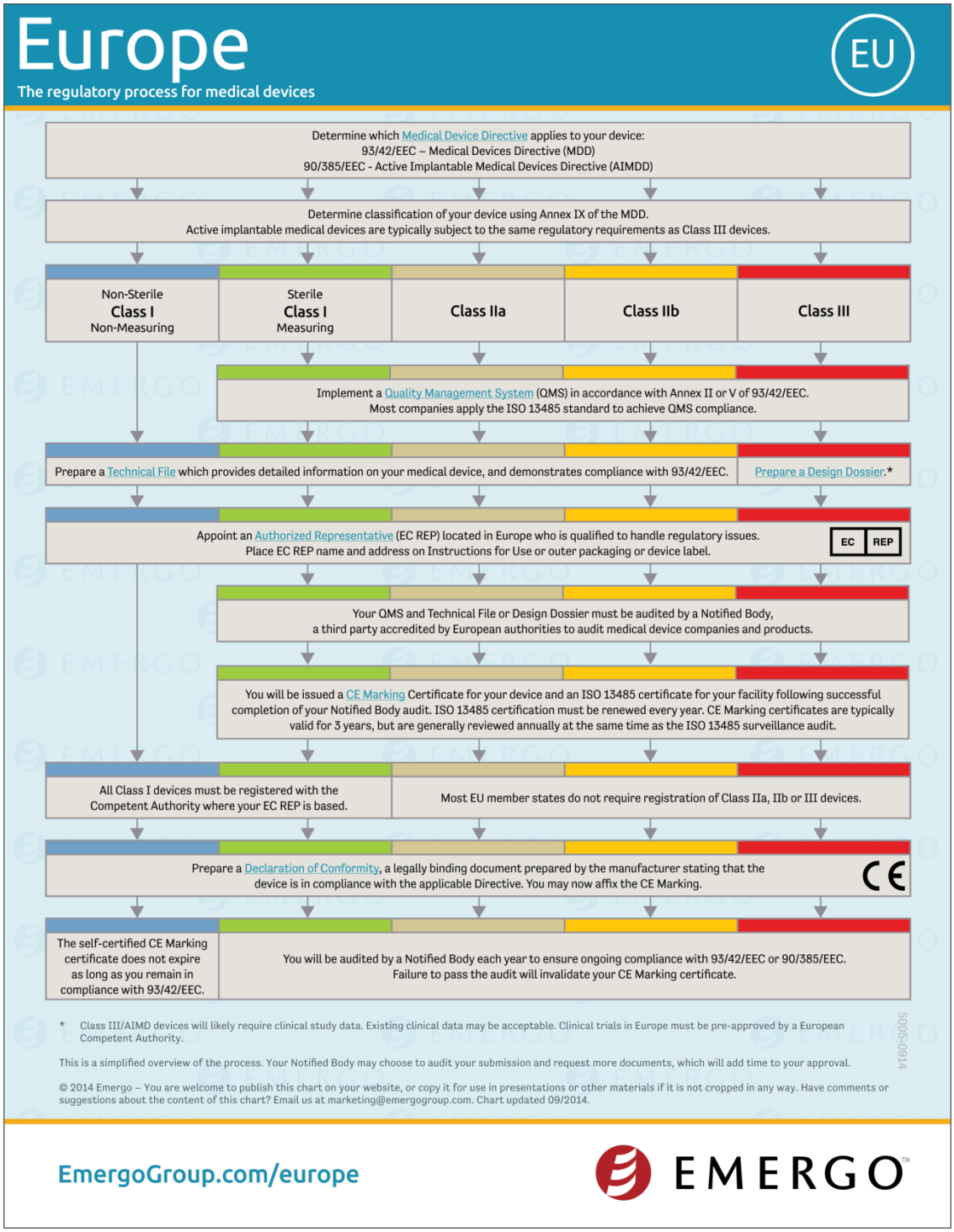
1. Classification of Your Medical Device
2. Identifying and Meeting Essential Requirements
3. Preparing Technical Documentation
4. Completing Required Conformity Assessments
5. Signing a Declaration of Conformity

APPENDIX B6

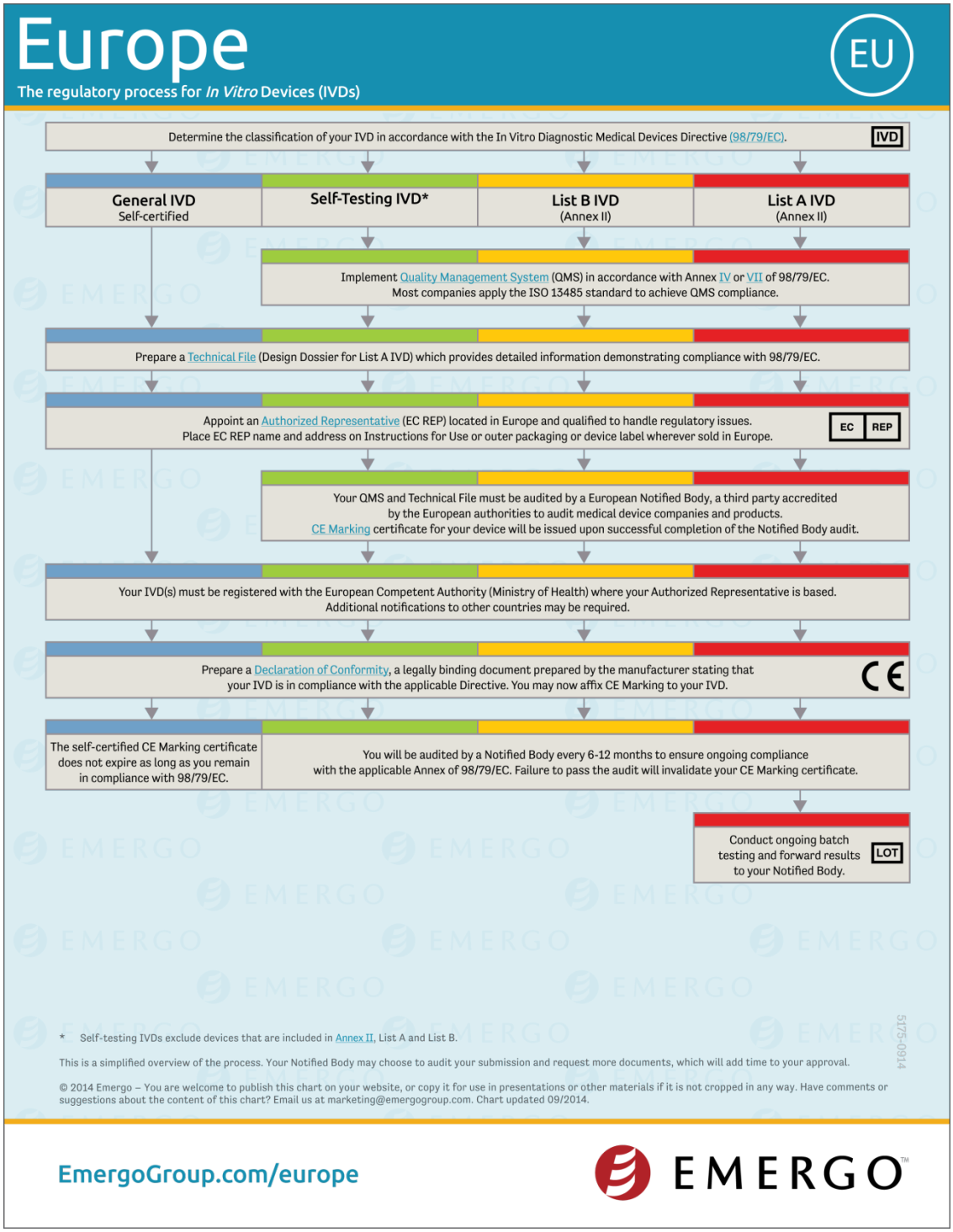
International Trade Administration: CE marking in 8 Steps

APPENDIX B7

Emergo Group Inc: Regulatory Process for Medical Devices



Emergo Group Inc: Regulatory Process for *in vitro* Devices (IVDs)



APPENDIX B8

QNET LLC: Acquiring CE Marking

How Do You Acquire CE Marking?

There are a series of steps outlined below. Depending upon your product and the nature of the risks it presents, there are several alternatives also noted that may apply to your situation.

● Determine if any directives apply to your product. If more than one applies you will have to comply with all of them.

● Determine the extent to which your product complies with the essential requirements for design and manufacturing in the applicable directive(s).

● Choose the conformity assessment procedure from the options called out by the directive for your product, often based on the level of risk.
Options for products with minimal risk include self-certification procedures where the manufacturer prepares required technical files, a declaration of conformity and affixes their CE Marking to their own product.
Options for products with greater risks can require tests, audits or additional certificates from a notified body.

● Select the applicable product standards and test methods for your product and select an independent accredited lab if the product testing is to be done externally.

● Establish an authorized representative for regulatory affairs in the European Union for your product. Most directives require that a manufacturer designate in Europe a representative to produce technical documentation in a timely fashion when called upon to do so.

The directives require for many products that a technical file be prepared by the manufacturer. The technical file holds information that verifies compliance with the essential requirements, that the testing was conducted properly and that the product complies with applicable directives and standards.

● Prepare a declaration of conformity what includes a list of the directives and standards that your product conforms to; product identification, the manufacturer's and the authorized representative name, address and signature.
The declaration of conformity contains information adequate for tracing the product back to the manufacturer or the authorized representative in the European Union.

● Affix the CE Marking to your product. There are specific requirements to adhere to in the CE Marking. These rules address the size and location of the marking, affixing the CE Marking to products, packaging and material or documents shipped with the product, and specific limitations on when and who is permitted to affix the CE Marking.

APPENDIX C1

List of National Standards Bodies

S/No	National Standards	National Standardisation Body	National Standards Body	Description
1	UNE	ANEOR	Spanish	Spanish Association for Standardisation and Certification
2	NF	AFNOR	French	French standards association
3	SR	ASRO	Romanian	Romanian Standard Association
4	БДС	BDS	Bulgarian	Bulgarian Institute for Standardisation
5	NBN	BIN	Belgian	Belgian Institut for Standardisation
6	BS	BSI	British	British Standards Institution
7	UNMZ	CNI	Czech	Czech Standards Institute
8	CYS	CYS	Cypriot	Cyprus Organisation For Standardisation
9	DIN	DIN	German	German Institute for

				Standardisation
10	DS	DS	Danish	Danish Standards Association
11	ΕΛΟΤ	ELOT	Greek	Hellenic Organisation for Standardisation
12	EVS	EVS	Estonian	Estonian Centre for Standardisation
13		IST	Icelandic	Icelandic Standards
14	LST	LST	Lithuanian	Lithuanian Standards Board
15		LVS	Latvian	Latvian Standards
16	MSA	MSA	Maltese	Malta Standards Authority
17		MSZT	Hungarian	Hungarian Standards Institution
18	NEN	NEN	Netherlands	Netherlands Standardisation Institute
19	I.S.	NSAI	Irish	National Standards Authority of Ireland
20	ÖNORM	ON	Austrian	Austrian Standards

				Institute
21	PN	PKN	Polish	Polish Committee for Standardisation
22		SEE	Luxembourg	Luxembourg organisation for Standardisation
23	SFS	SFS	Finnish	Finnish Standards Association
24	SS	SIS	Swedish	Swedish Standards Institute
25	SIST	SIST	Slovenian	Slovenian Institute for Standardisation
26	NS	SN	Norwegian	Standards Norway
27	SN	SNV	Swiss	Swiss Association for Standardisation
28	STN	SUTN	Slovak	Slovak Standards Institute
29	UNI	UNI	Italian	Italian Organisation for Standardisation

APPENDIX D1

Declaration of Conformity Template

Company Name Company Logo	**DECLARATION OF CONFORMITY**

Manufacturer:
Company Name
Company Address Line 1
Company Address Line 2
Singapore 123456
Tel: +65 1234 5678

Notified Body:
Notified Body Company Name
Company Address Line 1
Company Address Line 2
Tel: +00 (0) 24 680 1234
Fax: +00 (0) 43 210 8642

European Representative:
EC REP Company Name
Company Address Line 1
Company Address Line 2
Tel: +00 (0) 12 345 6789
Fax: +00 (0) 98 765 4321

Medical Device(s):

1. Name of product

We herewith declare that the above-mentioned product meets the provisions of the Council Directive 93/42/EEC (MDD). All supporting documentation is retained under the premises of the manufacturer.

Device Classification: Class__(Rule__), _____ device

Standards Applied: International Standards or
Harmonized Standards

Decision according to Annex___of Council Directive 93/42/EEC concerning medical devices

Place: Company Name, Country

Date: Month Day, Year (e.g. November 12, 2015)

Signature:

Name: Name of Manufacturer
Job Title of Company Name