TAMPERE UNIVERSITY OF TECHNOLOGY

LINDA KELLBERG

REGULATION BASED PRODUCT DEFINITION FOR AN IMPEDANCE PNEUMOGRAPHY MEASURING SYSTEM

Master of Science Thesis

Examiners: Professor Jari Viik,
University Lecturer Juha Nousiainen
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ABSTRACT

TAMPERE UNIVERSITY OF TECHNOLOGY
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Producing medical devices for commercial use within the European Union (EU) is a highly regulated process. The related regulation mainly consists of three medical device directives developed by the European Commission: the Medical Device Directive (MDD) 93/42/EEC, directive 90/385/EEC concerning active implantable medical devices, and directive 98/79/EC covering devices for *In Vitro* examination of specimen, as well as the related guidance documents i.e MEDDEVs. Additionally, medical device manufacturers are encouraged to utilize directive documents crafted and published by specialized organizations and harmonized European standards to ensure and facilitate the fulfilment of the objectives set by the directives.

The Impedance Pneumography (IP) measuring system is qualified as a medical device and has to be designed and manufactured according to the requirements set out in the MDD. Accordingly, the manufacturer has to design and implement the related processes, and establish adequate documentation on the development of the system beginning from the very definition of the product. The definition should include the intended purpose of the system, its qualification accordingly, and classification according to the classification rules presented in the MDD. The manufacturer also has to identify the other EU regulations and/or directives applicable to the product and any relevant harmonized standards accordingly, as they both increase the amount of individual requirements directed to the product and help to create frames for the design specifications.

The objective of this Master of Science Thesis is to create an initial product definition for the IP measuring system in accordance with the MDD. The definition will cover the intended purpose of the product, its qualification accordingly and its classification according to the MDD classfication rules. The Thesis will also define other EU directives and the harmonized standards applicable to the design and development of the system. Furthermore, the Thesis will provide an initial assessment of the feasibility of the product and an initial requirements definition for the solution found most desirable by the becoming manufacturer.

TIIVISTELMÄ

TAMPEREEN TEKNILLINEN YLIOPISTO
Sähkötekniikan koulutusohjelma
KELLBERG, LINDA: Impedanssipneumografian mittaamiseen tarkoitetun lääkinnällisen järjestelmän säännösperusteinen tuotemäärittely
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Lääkinnällisten laitteiden tuottaminen kaupallisiin tarkoituksin Euroopan Unionin (EU) alueella on säännöstelty prosessi. Prosessiin liittyvät viranomaismääräykset koostuvat pääasiallisesti kolmesta Euroopan komission julkaisemasta direktiivistä: lääkintälaite- eli MD-direktiivi 93/42/ETY, direktiivi 90/385/ETY koskien aktiivisia lääkinnällisiä laitteita ja direktiivi 98/79/EY liittyen *In Vitro* diagnostiikkaan tarkoitettuihin laitteisiin, sekä niihin liittyvistä Euroopan komission julkaisemista ohjeellisista dokumenteista. Edellisten lisäksi valmistajia kehotetaan hyödyntämään tiettyjen organisaatioiden tuottamia ohjeellisia dokumentteja sekä harmonisoituja standardeja direktiivien asettamien tavoitteiden saavuttamiseksi.

Impedanssipneumografian (IP) mittaamiseen tarkoitettu järjestelmä luokitellaan lääkinnälliseksi laitteeksi, joka on suunniteltava ja valmistettava MD-direktiivin vaatimusten mukaisesti. Valmistajan on suunniteltava ja toteutettava viranomaismääräysten mukaiset järjestelmän valmistukseen liittyvät prosessit ja niihin liittyvä dokumentaatio alkaen tuotteen suunnittelun lähtötiedoista. Tiedot koos-tuvat mm. järjestelmän aiotusta käyttötarkoituksesta ja sen määrittelystä käyttötarkoituksen mukaisesti sekä järjestelmän luokittelusta MD-direktiivin luokitussääntöihin perustuen. Valmistajan on myös tunnistettava tuotteeseen liittyvät muut EU-säädökset ja/tai -direktiivit sekä harmonisoidut standardit heti suunnittelun alkuvaiheessa, koska ne sekä lisäävät tuotteeseen kohdistuvien vaatimusten lukumäärää, että auttavat luomaan raamit tuotteen käytännön suunnittelulle.

Työn tavoitteena on tuottaa alustava MD-direktiivin mukainen tuotemäärittely IP-mittausjärjestelmälle kaupallistamistarkoituksiin. Tuotemäärittely kattaa tuotteen valmistajan tarkoittaman käyttötarkoituksen ja tuotteen määrittelyn sekä tuotteen luokittelun MD-direktiivin luokitussääntöjen mukaisesti. Työ sisältää sellaisten direktiivien ja harmonisoitujen standardien määrittelyn, joita voidaan pitää oleellisina tuotteen suunnittelulle ja valmistukselle. Lisäksi, työ kattaa tuotteen käytettävyyden arvioinnin ja käytettävyydeltään parhaaksi arvioidun ratkaisun alustavan vaatimusmäärittelyn.

PREFACE

This Master of Science Thesis was commissioned and funded by the Department of Electronics and Communications Engineering at Tampere University of Technology. The supervisor for this Thesis was Professor Jari Viik.

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Finally, I want to express my deepest gratitude to the three very special persons without whose support this could not have been done: to my wonderful parents Anneli and Juhani for always believing in me and to my beloved Ilari for always being there.

Tampere, 13 February 2014

Linda Kellberg

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ABBREVIATIONS

A	Applicable
AIMDD	Active Implantable Medical Device Directive
BMI	Body Mass Index
CA	Competent Authority
CE	Conformité Européenne (European Conformity)
CEN	European Committee for Standardization
CENELEC	European Committee for Electrotechnical Standardization
DA	Designating Authority
DDS	Device Design Specification
DoC	Declaration of Conformity
EC	European Community
ECG	Electrocardiograph
EEA	European Economic Area
EEC	European Economic Community
EN	European Standard
ESO	European Standardization Organization
ETSI	European Telecommunications Standards Institute
EU	European Union
FDA	Food and Drug Administration (US)
FICORA	Finnish Communications Regulatory Authority
FiHTA	Finnish Health Technology Association
FRD	Functional Requirement Document
GHTF	Global Harmonization Task Force
hEN	Harmonized European Standard

IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulators Forum
IP	Impedance Pneumography
ISO	International Organization for Standardization
ITU	International Telecommunication Union
IVDMDD	*In Vitro* Diagnostic Medical Device Directive
MDD	Medical Device Directive
MPD	Medicinal Products Directive
MRD	Market Requirement Document
MRS	Market Requirement Specification
NA	Not Applicable
NANDO	New Approach Notified and Designated Organizations
NB	Notified Body
OJEU	Official Journal of the European Union
PCB	Printed Circuit Board
QMS	Quality Management System
QS	Quality System
RoHS	Restriction of Hazardous Substances
SESKO	Electrotechnical Standardization Association (Finnish)
SFS	Finnish Standards Association
SG	Study Group
TRS	Technical Requirement Specification
Tukes	Finnish Safety and Chemicals Agency
URS	User Requirement Specification
US	United States
Valvira	(Finnish) National Supervisory Authority of Welfare and Health
WHO	World Health Organization

1. INTRODUCTION

Impedance Pneumography (IP) is a non-invasive measurement technique that is used for the measurement of various physiological volume changes. For example, it is often used to describe a method called Impedance Plethysmography conducted for indirect assessment of respiration by measuring the volume changes of the lung. The technique can also be described as a measurement of thoracic bioimpedance. [42, pp. 166, 168-169]

The measurement of thoracic bioimpedance for the assessment of respiration is based on the measurement of the electroconductivity of human thorax and its changes over respiration. As air is a poor conductor of electricity, whenever the patient inhales and their lung fill up with air, the electroconductivity decreases and related bioimpedance increases, respectively. Accordingly, over the exhalation the bioimpedance decreases in proportion to the amount of air leaving the lung. [42, pp. 168-169] By measuring the lung volume changes over respiration, healthcare professionals are able to make clinical assessment of the condition of the patient's lung.

The measurement is done using two or four electrodes depending on the chosen measurement configuration, as shown in Fig. 1.1. First a small alternating current is injected to the patient's thorax via a pair of electrodes. Secondly, the resulting response is measured as a potential difference between a pair of electrodes, respectively. Finally, the thoracic bioimpedance is derived from the known current and measured voltage using the Ohm's Law. In the four-electrode measurement (Fig. 1.1B) the current is injected via a pair of electrodes i.e. the driver electrodes and the potential measured between another pair i.e. the receiver electrodes, whereas in a two-electrode measurement (Fig. 1.1A), the same electrode pair is used for both procedures. [42, pp. 168-169]

The IP measuring system is used for the assessment of human respiration based on the volume changes in the lung. It is intended to be used as a diagnostic aid to support decision making in the diagnosis and management of childhood asthma. The current measurement configuration includes a measuring device, related accessories and computer software designed based on previous research by Vuorela et al [44] on long-term recording of physiological signals using a portable signal recorder, and by Seppä et al on the assessment of pulmonary flow using IP [34], on suppressing

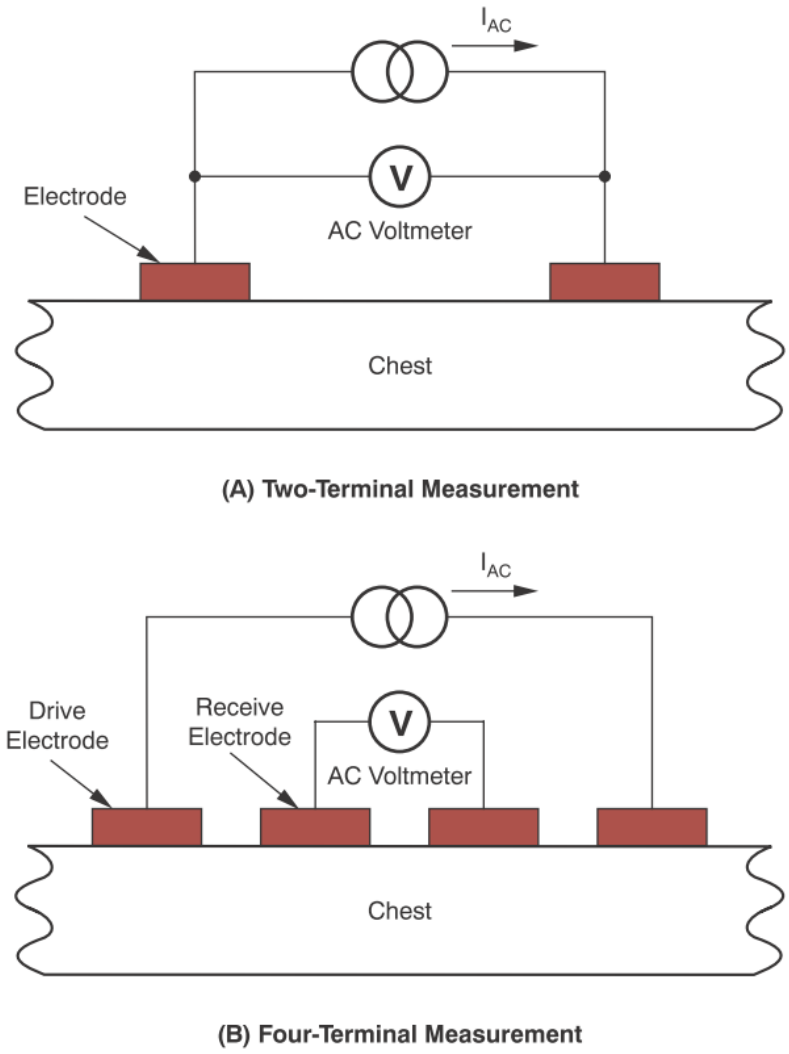

Figure 1.1: The A) two-electrode configuration and B) four-electrode configuration for an IP measurement (modified from [24, p. 1]).

cardiogenic oscillations in IP [32], and on the effects of electrode configuration to the linearity of IP [31]. In addition, a clinical research on the system has been conducted [33].

The measuring device is portable and intended to be used for a continuous IP measurement of several hours using the four-electrode measurement configuration. The device generates a small current that is injected to the patient's thorax, measures the resulting voltage and converts the known quantities to a continuous impedance signal. In addition, the device measures single channel electrocardiograph (ECG; ECG measurement via one electrode pair) for signal processing purposes and acceleration to record position and activity related data. The functions of the measuring device are controlled by embedded software incorporated into the device.

The measurement data is uploaded to the computer software. The software is

used to process the impedance signal and to remove any artefacts caused by cardiac activity. After processing the signal, the software provides the user with an illustration of a cleaned, ideally continuous impedance signal indicating the respiratory functions of the patient. Prototypes of the measuring device and the computer software have already been designed and manufactured and their performance is currently being investigated to prove their applicability to their intended purpose.

The IP measuring system is commercialized as a medical product which essentially affects the related processes resulting in the market approval of the system. Accordingly, commercialization of medical systems and/or devices is a highly regulated process which includes the involvement of various different regulatory authorities and numerous regulations and requirements for both the product and the manufacturing company.

The current solution for the IP measuring system does not fulfil the European regulatory requirements for medical devices and is thus, not allowed to be released on the European (or any other) market. The system needs to be 'redesigned', developed, manufactured and tested according to the Finnish and European legislation beginning from the very definition of the product. In addition, the manufacturing company needs to develop and document any related and other relevant processes according to the same regulations before they can function commercially as a medical device manufacturer.

The Study discusses the regulatory aspects of the commercialization process of medical devices within the EU falling under the scope of the MDD. The Study mainly concentrates on the CE (Conformité Européenne, i.e. European Conformity) marking process and related activities from the perspective of a Finnish medical device manufacturer. Accordingly, the Study does not address any national differences in medical device regulations nor regulation by the Food and Drug Administration (FDA) of the United States (US), for example.

The objective of the Study is to increase the understanding on the regulatory requirements for the IP measuring system, and to produce an initial product definition for the system for regulatory purposes. Consequently, the Study results in defining the intended purpose of the system and its product category, its classification with respect to the EU medical device regulations and product specific regulatory requirements, including any relevant directives and applicable European standards for particular product features and for the processes required from the manufacturer. Finally, the product definition, in addition to particular business related considerations of the design of the system are documented in a so called Feasibility Study document based on which an initial requirements specification is created.

The Study is divided into six Chapters. The first Chapter contains an introduction to the topic including the motivation behind the Study. Chapter 2 discusses the

regulatory framework of product development and commercialization, the related authorities and their relationship within Finland and the EU, particularly concentrating on that of medical device design, development and manufacturing. The third Chapter concentrates on the CE marking process of medical devices in more detail. Chapter 4 compiles the results of the Study concerning the IP measuring system, the applicability and adequacy of which are further discussed in Chapter 5. Chapter 5 also addresses the nature of medical device regulations and some expected changes within the related regulatory framework. Finally, the Study is concluded in Chapter 6.

2. REGULATORY FRAMEWORK FOR MEDICAL DEVICE DEVELOPMENT IN THE EU

The chapter discusses the regulatory framework for product development within Finland and the EU, including the related regulatory authorities, their roles and mutual hierarchy. The latter sections of the chapter particularly address the development of medical devices.

2.1 General

[16, pp. 5-6] According to the World Health Organization (WHO), medical devices were one of the fastest growing areas of industry worldwide in 2003 [45]. Similarly, in April 2013 Finnish Health Technology Association (FiHTA) announced that the export of Finnish healthcare technology industry had increased 23 per cent over 2012, as shown in Fig. 2.1 now covering 38 per cent of the overall export of Finnish high-technology [19].

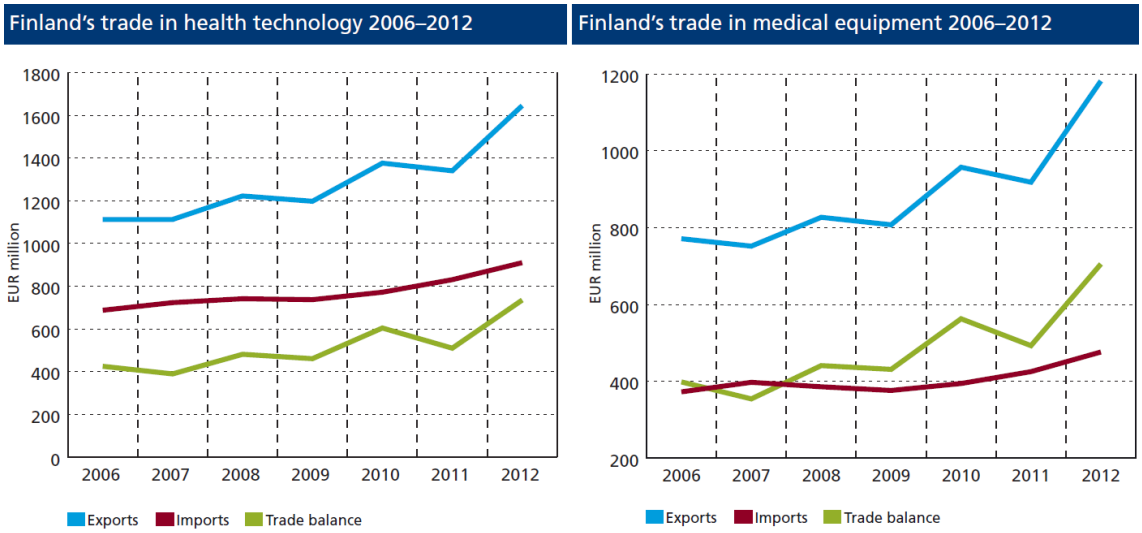

Figure 2.1: Finland's export in health technology and in medical equipment in particular between 2006 and 2012 (modified from [19, pp. 2-3]).

As the knowledge and understanding of diseases, the manners of their progression and of the impact they have on human life increases, more attention is directed

to their earlier detection and diagnosis, control and monitoring. Accordingly, clinicians are keen to cooperate with research and industry, new medical innovations are created and new applications for existing solutions are invented. Modern technologies challenge the conventional methods in such areas as usability, efficiency and accuracy, aiming to provide new perspective on health and related parameters in compact and feasable manner.

Medical devices are used for humans and often by other humans which forms the sole most important reason for the vigorous regulatory control of their safety and performance. Understandably, the establishment of new, unfamiliar technologies generates a need for new regulations to create frames for the safety and performance required from these approaches. Accordingly, the design, develpment, publishment and maintenance of medical device regulations is an ongoing process aiming at more and more detailed and comprehensive control over the development of the overall variety of medical devices. As a consequence, the medical device industry is encouraged to establish close collaboration with the related regulatory authorities to maintain the innovativeness within their field and to ensure their success also in the future. [20]

2.2 Regulations for Product Development and Commercialization in General

Within the EU, *the manufacturer* is defined as a natural or legal person who bears the sole responsibility for the design, manufacture, packaging and labelling of a product under their own name, regardless of whether these activities are performed by that person themselves or by a third party on behalf of the manufacturer. As the legal responsibility cannot be delegated, the manufacturer is also overall responsible for the operations carried out by their suppliers and subcontractors that affect the manufacturer's product. [16]

Accordingly, when commercializing their product within the EU, the manufacturer is obliged to take into consideration various different regulations all interrelated, but not necessarily fully consistant with each other. Depending on the place of location of the manufacturer and the determined market area(s) of their product, the regulatory frame of their operations may include various different requirements set down by national authorities, the EU and other regulatory organizations. [20]

2.2.1 EU Legislation and National Laws

The highest regulatory authority within Europe is the EU. The main executive bodies of the EU include the European Commission representing the interests of the EU en bloc, the Council of the EU representing individual Member States, and the

European Parliament representing EU citizens. The EU decision-making process is called 'codecision' in practise meaning that the European Commission prepares a proposal for new legislation and presents it to the European Parliament who, in conjunction with the Council, approves the proposal. [10]

Laws of the EU are implemented as acts available for the public through the official webpage of the EU, for example. The acts include different regulations, directives, decisions and recommendations that affect the Member States in different ways [14]. For example, EU regulations are binding acts that must be applied in their entirety across the EU. EU directives, on the other hand, are put into effect by the Member States by implementing them into their national legislation under the surveillance of national regulatory authorities. EU decisions bind only those to whom they are addressed to and are directly applicable, whereas recommendations are non-binding and thus, bear no legal obligations. Accordingly, recommendations are published mainly to provide information and suggestions to be used as guidance, when found appropriate. [14]

Fulfilment of the EU objectives is supervised by related national authorities and certain third parties specifically appointed for the job. Accordingly, the Conformity Assessment Bodies i.e. Notified Bodies (NBs) work EU-wide supervising the compliance of specific products and processes with the related EU objectives.

Notified Bodies

The EU Member States are obliged to designate NBs to perform conformity assessment for the directives within the scope of their operation. The NBs are notified to the European Commission and listed in the New Approach Notified and Designated Organizations (NANDO) database including their NB number, place of operation and scope of expertise, for example. All NBs within the same scope are to be considered equal and no more than one can be used for the same purpose. [8, p. 8]

The operations of the NBs are regulated and they must conform to certain specified requirements including technical competence, impartiality and confidentiality. They are subjected to the Commission's regulations and recommendations, as well as particular standards defined in EU legislation. [8, p. 8] Accordingly, the manufacturer may benefit greatly from studying the NB regulation and recommendations in addition to those directly aimed at their own activities, as those documents often include guidance on how the inspections and related activities are conducted in practice, and on what issues the NB is to pay special attention to [35].

The NB used is chosen by the manufacturer. Accordingly, the manufacturer can choose any NB established within the NANDO whose scope covers the manufacturer's product (e.g. machinery, pressure equipment, medical devices, active implantable medical devices). Other features possibly affecting the choise of the

NB include their location (the manufacturer is obliged to cover their travelling and accommodation costs) and possible prior experiences of using the particular NB. [20][35]

The work of an NB includes the inspection and examination of the manufacturer's product and its design and manufacture, after which the NB either does or does not confirm the alleged compliance. It is only after a positive statement from the NB that the manufacturer can declare the conformity, affix the CE marking, if required, and is legally allowed to place their product on the market. However, depending on the field of the solution and the risks associated with the product, not all products need to be inspected by an NB (e.g. Class I medical devices), because of which an understanding of the level of control and supervision required by the authorities should be fully established prior to any attempts to penetrate the EU market. [8, p. 8]

2.2.2 Standardization

Standard is defined as a document providing common requirements, specifications and guidelines which can be used to ensure that materials, products, processes and services are fit for their intended purpose. Accordingly, they are not legally binding and their use is thus, not mandatory. [26]

Standards are crafted and published by acknowledged standardization organizations on international, European and national level, and often inspected on several occasions by the related standardization bodies to confirm their compliance with any relevant regulations. Consequently, the use of appropriate standards applicable to the operational field of the manufacturer and the particular product or solution is strongly recommended [2][20] to ensure the conformity of the manufacturer's processes and products with the regulatory requirements, and to standardize the operations and activities of different actors within the same field of industry. [26]

Levels of Standardization

There are three essential levels of standardization: international, European and national level. The levels and related authorities from Finnish perspective are shown in Fig. 2.2. Internationally, the most extensive standardization body is the International Organization for Standardization (ISO) who develops voluntary standards for international use. In addition, the International Electrotechnical Commission (IEC), one of the most important collaborators of ISO, concentrates on standardization of devices containing electronics and using, or producing electricity. Finally, the International Telecommunication Union (ITU) specializes in standardization of information and telecommunications tecnologies. [27][41]

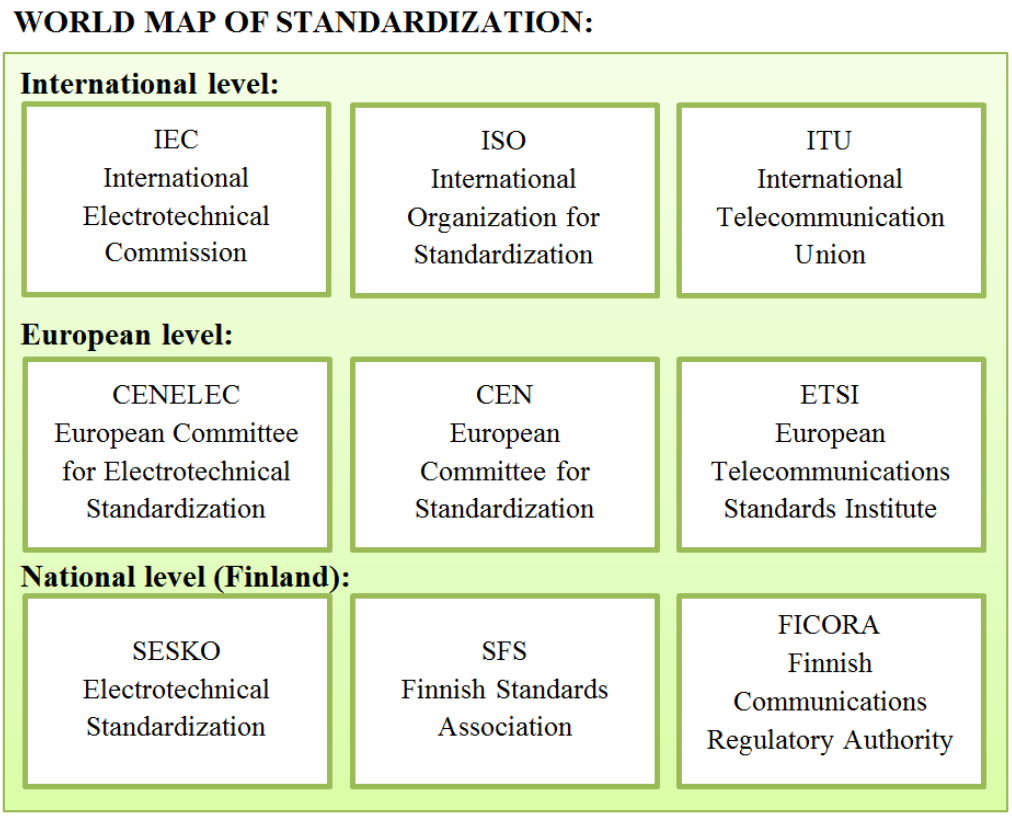

Figure 2.2: Levels of standardization and related authorities from the perspective of a Finnish manufacturer (modified from [41]).

All international standardization bodies collaborate with their European counterparts i.e. the European Standardization Organizations (ESOs). ESOs consist of the European Committee for Standardization (CEN), the European Committee for Electrotechnical Standardization (CENELEC) and the European Telecommunications Standards Institute (ETSI). CEN and its sister organization CENELEC correspond the ISO and IEC providing European standards and technical specifications within the field of their expertise. ETSI, on the other hand, produces global standards for information and communications technologies. Additionally, CEN, CENELEC and ETSI collaborate with the national standardization bodies working within each EU Member State who both confirm the standards published by the ESOs as national ones and produce standards of their own. [12][41]

In Finland the main standardization body is the national Finnish Standards Association (SFS). The main purpose of the SFS is to direct and coordinate the production of and to confirm national i.e. Finnish standards. In addition, SFS cooperates with the ESOs and international standardization organizations, representing Finland within their activities. Accordingly, the SFS is responsible for incorporating the European and international standards, such as those of the CEN, into the

Finnish state-of-the-art guidelines of the desing and development of different products. Finnish national standards for electrotechnical engineering are provided by the Electrotechnical Standardization Association (SESKO), a member of the SFS, and for telecommunications by Finnish Finnish Communications Regulatory Authority (FICORA). [41]

In order to determine the standards the manufacturer can employ in their operations, it is essential for them to understand the conceptual difference between standards crafted and/or adopted by different organizations on different levels of standardization. International standards are crafted and published by international standardization bodies, and equipped with a prefix 'ISO' or 'IEC', for example, to indentify the organization behind the publication. These standards are created for universal application within their scope, based on global expert opinion and in consensus with stakeholders, in order to overcome technical barriers in trade due to differences among technical regulations and standards developed separately within each individual state, for example. [26]

International standards are often adopted as European and/or national standards by related standardization bodies. [41] Accordingly, CEN, CENELEC and ETSI craft and publish European standards equipped with a prefix 'EN' aiming to facilitate the concept of Single European Market. ESOs also confirm international ISO and IEC standards as European, either without changes or with minor modifications if found necessary in order for the standard to fit better in the European legislation. In addition, national members of the ESOs', such as the SFS, are required to adopt the EN standards as such thus, automatically confirming them as national, e.g. SFS standards. [41]

The EN standards codify the best European practices and are usually considered as the European state-of-the-art within their scope of application. [13] However, the employment of any of the abovementioned standards alone is not sufficient to prove the product's conformity with the EU legislation. For the purpose of proving compliance with the EU requirements the manufacturer must recognize the *harmonized* European standards applicable to their product. [11]

Harmonized Standards

The ESOs cooperate with the European Commission and the European Free Trade Association facilitating the implementation of the European Commission directives. To support the EU policies and legislation, the ESOs develop and adopt European standards on the Commission's request, by the means of 'standardization mandates' (i.e. request for standardization) creating *harmonized European standards* (hENs), also referred to as harmonized standards, officially recognized by the EU. [13]

The hENs always include a so called *Annex Z* (see Fig. 2.3 for example) (e.g.

Annex ZZ, ZA, ZB, ZC, etc.) that discusses the conformity of the standard with related European legislation (e.g. particular directives). Hence, they provide a coherent technical instructions for manufacturers according to which they can both design and develop their product and test its performance being certain that it conforms to the related EU requirements. [11][36]

Annex ZA
(informative)

Relationship between this International Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical devices

This International Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on Medical devices.

Once this International Standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this International Standard given in Table ZA.1 confers, within the limits of the scope of this Intenational Standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this International Standard and Directive 93/42/EEC on Medical devices

Clause(s)/subclause(s) of this International Standard	Essential Requirements (ERs) of Directive 93/42/EEC on Medical devices	Qualifying remarks/notes
4, 5, 6, 7	Annex I: 7.1, 7.2 and 7.5	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this International Standard.

Figure 2.3: The Annex ZA of standard EN ISO 10993-1 (2009) concerning the standard's relationship with the directive 93/42/EEC (modified from [38, p. 4]).

References to the effective hENs are published in the *Official Journal of the European Union (OJEU)* (formerly known as the Official Journal of the European Community). OJEU can be found from the official webpage of the European Commission where the standards are divided into product categories (e.g. cosmetics products, medical devices, etc.) according to their scope. Accordingly, whether the effective version of the international standard based on which the hEN has been created changes or not, the version required by the European regulatory authorities is always the one mentioned in the OJEU. [11]

2.3 Regulations for Medical Device Design and Development

Within the EU, a medical device is defined as follows.

> "'Medical device' means any instrument, apparatus, appliance, software, material, or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
>
> - diagnosis, prevention, monitoring, treatment or alleviation of disease,
>
> - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
>
> - investigation, replacement or modification of the anatomy or of a physiological process,
>
> - control of conception,
>
> and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

[16, pp. 5-6] Based on the definition, it is fairly easy to understand the relevancy of adequate and comprehensive regulatory control within the design and development of medical devices, as well as the potential worst case scenario resulting from insufficient or faulty measures within the related processes. Accordingly, there are various authorities who take part in medical device development in different way to ensure their safety and performance before their market release.

Basic structure of medical device regulation and the hierarchy between related authorities in Finland and the EU is shown in Fig. 2.4. Accordingly, a Finnish medical device manufacturer is primarily obliged to obey the Finnish legislation and the instructions provided by the Finnish National Supervisory Authority of Welfare and Health (Valvira). Valvira acts as both the Designating Authority (DA) and the Competent Auhtority (CA) of medical devices' design and development in Finland. Accordingly, they have the legal authority to firstly, appoint Finnish NBs and, respectively, remove their notification rights, and secondly, to monitor and supervise the conformity of medical devices to related legislation and regulations, as well as their marketing to ensure their adequote performance and patient safety. [43]

Furthermore, in order to be legally allowed to place their product on the European market, the manufacturer has to follow the EU legislation which, in the case of medical devices, primarily consists of three related directives all including *Annexes* that provide more specific instructions on the implementation of the regulation. Additionally, the European Commission publishes guidance documents i.e. MEDDEVs

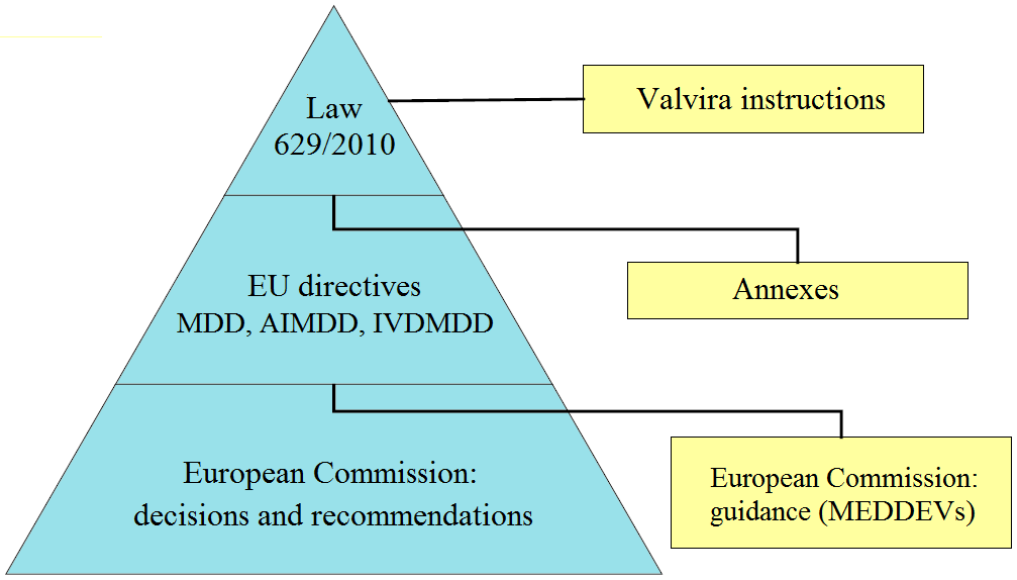

Figure 2.4: Regulatory framework for commercializing a medical device in Finland (modified from [29]).

to further help the manufacturer with the implementation. The European Commission may also provide decisions and other recommendations that can be used as directional when conducting state-of-the-art design and development of medical devices [14][35].

2.3.1 Medical Device Directives and MEDDEVs

Currently there are no active EU regulations that concern medical devices. However, there are three principal directives addressing the state-of-the-art in medical device design and development: the MDD 93/42/EEC, Active Implantable Medical Device Directive (AIMDD) 90/385/EEC and *In Vitro* Diagnostic Medical Device Directive (IVDMDD) 98/79/EC. All three directives have been incorporated into the Finnish legislation and put into effect in 2010 under the Medical Devices Act 629/2010 (Fin. Laki terveydenhuollon laitteista ja tarvikkeista). [37]

The AIMDD addresses medical devices that are powered by electricity or other external power source, introduced into the human body and intended to remain in their place after the implantation [15, p. 2], whereas IVDMDD only concerns devices intended to be used *In Vitro* (i.e. outside the human body) for the examination of specimen [17, p. 5]. All other medical devices, hereafter referred to as 'medical devices', fall primarily under the scope of the MDD.

Directives concerning medical devices do not cover medicinal products i.e. pharmaceuticals. Accordingly, such product are regulated by the Medicinal Products Directive (MPD) 2001/83/EC. However, there are *borderline products* that include

pharmaceuticals in their medical device -like operations. The MDD does provide some guidance on how to make the difference between these two product categories, but some devices may still require further examination of related guidance documents. As a general rule, a relevant product is regulated either by the MDD, the AIMDD or by the MPD, and not by all of them or by their combination. [5, p. 5].

The MDD was developed by the European Economic Community (EEC; 1957-1993), today known as the European Communities (EC), and initially implemented in 1993. The directive provides common guidelines for the medical device design and development within the European Economic Area (EEA) aiming to harmonize the laws concerning medical device design and development within Europe and thus, enable single market within the EU. The directive has been amended five times, most recently in 2007 by the directive 2007/47/EC and the compliance with the new requirements has been mandatory since 2010. [37]

Every medical device manufacturer producing devices within the scope of the MDD are legally obliged to follow the procedures and requirements described in the directive in order to be allowed to sell their product within the EU. The MDD determines the processes for designing, developing and manufacturing safe and reliable medical devices suitable for their intended purpose and their intended use environment. [16]

The main content of the MDD consists of the very definition of a medical device, device classification, the essential requirements concerning the features of the device design and development and related principles according to intended purpose of the device, and the procedures the manufacturer has to perform in order to show conformity of the device with the applicable requirements, including appropriate clinical evaluation and sufficient clinical data/evidence. The MDD also contains a reference to hENs officially recognizing their use in proving the product's conformity with the mentioned requirements. [16]

Classification of Medical Devices

According to its scope, the MDD covers a wide range of different products from hospital beds, blood bags and patient monitors all the way to medical software and bone cement, for example. Consequently, it is not economically feasible nor justifiable in practice to subject the development of all medical devices to the same amount of control. Thus, the directive provides the manufacturer with a graduated system of control where the level of control responds to the level of potential hazard inherent in a particular type of a device and is described using a risk-based classification system. [7, p. 4]

Within the EU, medical devices are divided into four separate classes: Class I for low risk devices, Class IIa for low to medium risk devices, Class IIb for medium to

high risk devices and Class III for devices presenting a critical risk such as death. Additionally, Class I medical devices are further divided into three groups: Class I, Class Im and Class Is separating such basic low risk devices as eye-test charts from those including a measuring function (*m*; e.g. a thermometer) [4, pp. 2-3] and those delivered in a sterile state (*s*; e.g. surgical gloves). Within Europe, the difference between the Classes I, Im and Is is essential to understand, as Class Im and Is devices are subjected to a sufficiently higher regulatory control than those of the basic Class I. [7, p. 5]

The classification of medical devices bases on the vulnerability of the human body taking into account different criteria determined in the MDD, including the duration of contact with the body (e.g. transient, short term or long term), the degree of invasiveness of the device (e.g. non-invasive, invasive, body orifice, surgically invasive or implantable) and the local versus systemic effect of the device (e.g. devices in contact with the central nervous or central circulatory system). [7, pp. 4, 7-10]

The classification of medical devices is done by the manufacturer based on the intended purpose of the product and according to the MDD. However, the authorities may challenge the reasoning behind the chosen device class and require justification for the manufacturer's decisions. Thus, depending on the statement of the NB, the manufacturer may have to change the product class according to the given NB instructions. [20]

Essential Requirements

All medical devices to be commercialized within the EU need to fulfil applicable essential requirements defined in the MDD (*Article 3* and Annex I) before they get a market approval. The requirements include both general requirements common to all medical devices and more specific requirements directed to certain types of products. The general requirements concern the basic concept of medical device design, development and performance addressing the manufacturer's processes in general, whereas the more specific requirements include those concerning particular features of medical device design and construction, such as chemical, physiological and biological properties, sterilization, environmental properties, measurement sensitivity, emission of radiation, use of an energy source, and information the manufacturer is obliged to provide the customer with. [16]

Essential requirements applicable and not applicable to a particular product are determined by the manufacturer based on the intended purpose of the device. When found not applicable, the manufacturer has to justify their decision to the authorities by related documentation. The fulfilment of the applicable essential requirements is validated via a specified conformity assessment procedure performed either by the manufacturer themselves (*self-declaration*) or by an NB, when required. [16]

Even though the MDD sets certain boundaries and requirements for the medical device design and development, it does not offer any ready solutions on how to accomplish the mandatory EU objectives. Because of this, the manufacturer is encouraged to utilize guidance MEDDEVs published by the European Commission in addition to and in combination with the directive. The MEDDEVs are intended to promote a common approach by manufacturers and the NBs involved in the conformity assessment procedures, and by CAs with safeguarding public health, by providing instructions on the implementation of the MDD. As the EU recommendations, the MEDDEVs are not legally binding, but intended to facilitate the uniformity of the solutions established by different medical device manufacturers and thus, the assessment of conformity. [3]

2.3.2 Guidance on Medical Device Regulations

The MDD and MEDDEVs, along with appropriate hENs provide a well-defined framework of requirements and guidelines on issues that a medical device manufacturer needs to resolve, verify and validate, and on processes that they need to implement. Nevertheless, nor the MDD or hENs offer instructions on how to succeed the required regulatory goals thus, letting the manufacturer to develop their own procedures. Because of the rigorous regulatory control, however, the development of fully congruent and acceptable processes is laborious, time-consuming and expensive hence, increasing the demand for more practical guidance on the implementation. Accordingly, international advisory bodies have been founded to provide assistance on transferring the regulatory requirements to specific actions. [25]

Global Harmonization Task Force (GHTF) was established in 1992 consisting of a voluntary group of representatives of national medical device regulatory authorities and the related industry from Europe, Asia-Pasific and the US. The main objective of the GHTF was to promote the uniformity of medical device regulations related to safety, efficiency, performance and quality, to enable the related technological innovations, and to facilitate the international trade. [25]

The 'executive body' of the GHTF consisted of five Study Groups (SG) concentrating on different aspects of the commercialization process of medical devices. The SG1 produced guidance documents on the general issues the manufaturer is required to consider prior to the product launch and the SG2 provided guidance on required manufacturer activities after the product is placed on the market, e.g. post-market surveillance and vigilance reporting. The SG3 concentrated on Quality Systems (QSs), SG4 on auditing, i.e. inspection practices of the regulatory authorities, and the SG5 provided guidance on clinical evaluation, including the documentation on the basic safety and essential performance of medical devices. [25]

GHTF was since permanently replaced by the International Medical Device Regu-

lators Forum (IMDRF) founded in 2011. The management committee of the IMDRF consists of regulatory officials from Australia, Brazil, Canada, Europe, Japan and the US, and the involvement of the Chinese and Russian authorities are currently being confirmed. The agenda of the IMDRF is similar to that of its predecessor aiming to provide guidance for harmonization and more comprehensive medical device design and development processes, increasing the patient safety and the efficiency of the related technologies. [25]

Even though the EU market is rather consistent when it comes to medical device regulations, the manufacturer is encouraged to study the national legislation of the target market(s) of their product in addition to the general EU acts, and not to rely solely on the concept of 'uniform regulation' within the EU. The legislation of the EU Member States cannot contradict that of the EU, but individual states can establish national laws indicating additional requirements for medical device manufacturers. For instance, the requirements for environmental design and of the sufficient clinical evidence may differ substantially between different European countries. [20]

3. COMMERCIALIZATION OF MEDICAL DEVICES IN THE EU

The chapter discusses the regulatory framework of medical device design and development in more detail and from a more practical point of view. The following sections especially address the CE marking process and related requirements, and processes through which the manufacturer can obtain the market approval for their product.

3.1 General

According to the related EU legislation, medical devices along with more than twenty other product categories, such as machinery, require CE marking before they can legally be released on the EU market. According to its definition, the CE marking indicates the product's conformity with the European legislation symbolizing the free marketability within the EEA. However, even though the CE marking is recognized worldwide, most market areas outside the EU have their own legislation and require additional procedures to prove the compliance of a medical device with their specific requirements. [8][20]

The main steps and general content of the CE marking process are described in Fig. 3.1. Accordingly, the process of affixing the CE marking begins from defining the particular product including its intended purpose, related main directive(s) and the device risk class. The manufacturer then determines any other directives, as well as hENs related to the product. The manufacturer is also encouraged to seek for any further regulatory or instructive statements provided by the EU and/or the European Commission, as mentioned previously. [8]

Next, the manufacturer establishes the essential requirements applicable to the product listed in the applicable directive(s) and makes a decision on what conformity assessment procedure to follow in order to prove the compliance with the defined requirements. The conformity is assessed according to the chosen procedure either by the manufacturer themselves (e.g. self-declaration for Class I medical devices) or by an NB, who inspects the product, including the technical documentation and the manufacturer's processes, when required, and either confirms or denies the conformity. [8]

After a successful assessment, the manufacturer draws up a Declaration of Con-

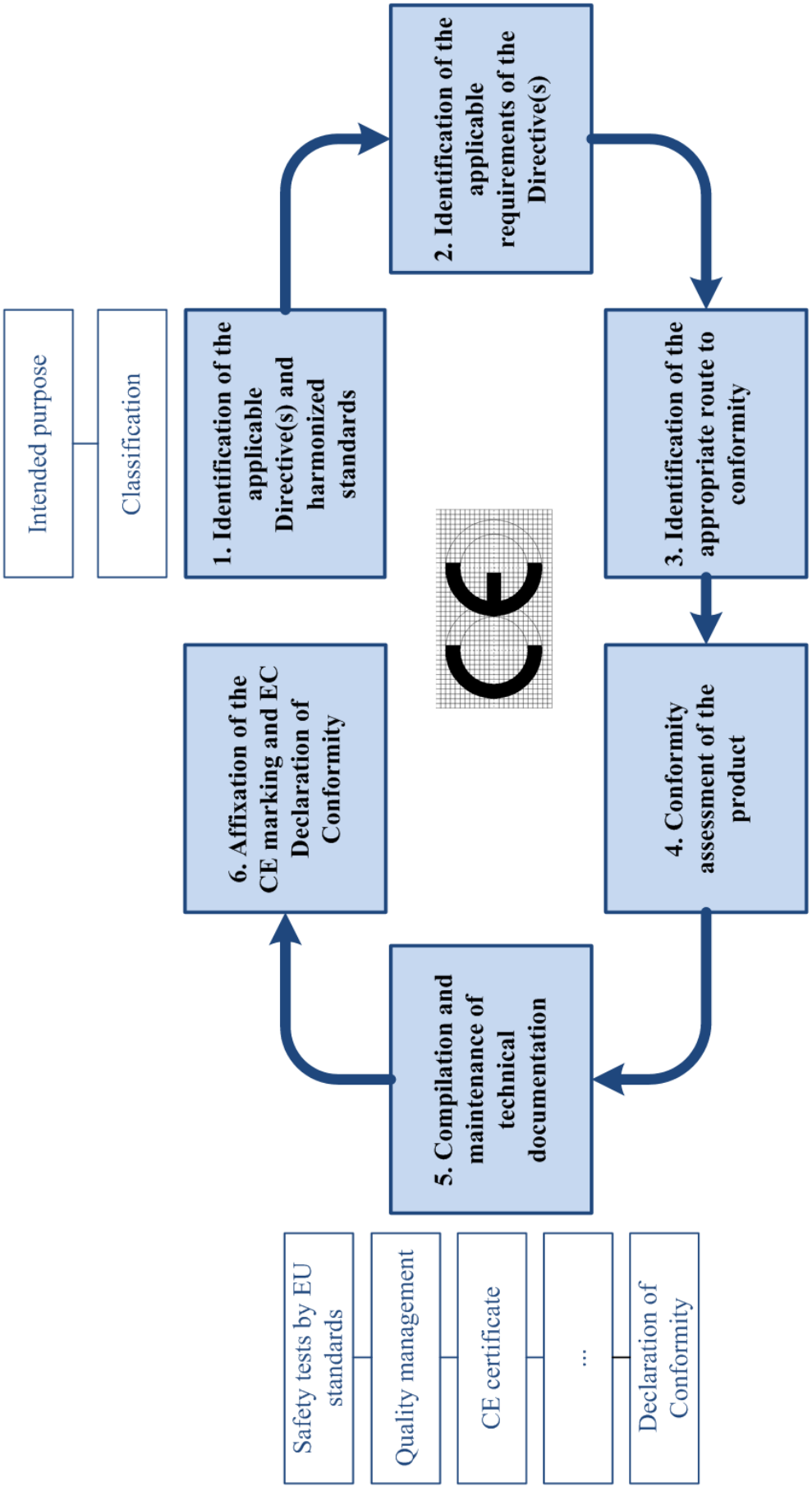

Figure 3.1: CE marking process (modified from [8] and [16]).

formity (DoC). The DoC is a document containing all relevant information about the manufacturer (e.g. who and where), the product or product*s* the DoC refers to, the directives and standards the product conforms to, a reference to the location of the related test results, and details of the responsible person in the manufacturing company. There are no specified form for the DoC, but some default formats are widely available. [16, p. 33]

After submitting the DoC, the manufacturer can affix the CE marking on their product and release it on the EU market. Consequently, by providing the authorities with the DoC, affixing the CE marking and preparing and maintaining the technical documentation, the manufacturer guarantees on their sole responsibility that their product conforms to all relevant EU regulations and that the necessary assessment(s) has been completed. [8] Affixing of the CE marking under false pretences will lead to a product recall and in some cases to further legal actions against the manufacturer. [16]

3.2 Product Definition

In order to establish the relevant regulation and the required amount of internal and external control for a particular medical device, the manufacturer needs to define their device and any related articles in detail. For example, the applicable national legislation and directive(s) including essential requirements are defined based on the intended purpose of the product. Accordingly, the device risk class determines the appropriate conformity assessment procedures to be followed and whether or not a third party (NB) evaluation is required. Depending on the conformity assessment procedure the manufacturer is required and/or decides to follow, they have to establish different certified procedures concerning the quality and risk management, for example, and controlled processes for related documentation and document control in order to fully conform to medical device regulation. [8]

3.2.1 Intended Purpose

According to the EU legislation, the intended purpose of a medical device means the use for which the device is intended according to the data provided by the manufacturer on the labelling of the device, in the instructions for use and/or in the material used in advertisement [16, p. 7]. Intended purpose is sometimes referred to as Intended Use or Indications for Use, both rather used within the US than in the EU. [21]

The EU does not provide detailed instructions on what the definition of the intended purpose of a product should include. However, to ensure the correct use of a medical device, the definition of its intended purpose has to incorporate at

least the condition the device is intended to address (e.g. asthma) and its main functions (e.g. recording and processing of specific data for diagnostic purposes), its intended users (e.g. clinicians), intended use environment (e.g. healthcare facilities), and target population (e.g. adults). [20] In addition, the intended purpose should discuss any possible restriction for use such as race, height, weight or percentage of fat or Body Mass Index (BMI), if found appropriate, patients with special needs (e.g. children), and so forth. If other devices or accessories are required for adequate functioning of the medical device, their joint use must be indicated in the intended purpose of the medical device. Furthermore, if the abovementioned accessories are produced by the manufacturer, their intended purpose should also indicate the joint use, respectively. [28]

Before their market release, medical devices are always tested against their intended purpose over a process called design and development validation. In addition, the validation of a medical device always includes clinical evaluation of the product and may sometimes require additional clinical data obtained via more comprehensive clinical investigation within the intended use environment, users (if other than target population) and target population (i.e. patients). Accordingly, the more general description of the intended purpose is provided, the more extensive set of validation procedures are required, as the validation should cover all possible use cases. [28] For example, adequote performance of a device intended to be used on 25-50 year-old Caucasian females is likely to require sufficiently less clinical evidence than that claimed to perform well for all adults.

3.2.2 Product Qualification and Classification

After the manufacturer has determined the intended purpose of their product, they should have a good idea whether the product can be considered as a medical device or not based on the definition in the MDD. However, the manufacturer should provide a documented reasoning for the qualification in a case the authorities challenge their view. This can be done using a table such as Table 3.1 containing the definition of a medical device as it is given in the MDD. [28] As long as even one section of the definition of a medical device is found applicable to the product, the product is qualified as one, and must be designed and manufactured accordingly.

Most equipment used in heathcare consist of numerous different components that are all required to obtain the desired intended purpose. However, not all the components are necessarily medical devices i.e. do not fulfil the abovementioned definition. For example, an electronic device that is used to measure and record physiological signals, but which does not provide any other functions, such as signal monitoring or analysis, is not a medical device by definition. These devices are rather defined as accessories meaning any article intended by the manufacturer to be used together

Table 3.1: Qualification of a product according to the MDD (A = Applicable, NA = Not applicable) [16].

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease		
prevention of disease		
monitoring of disease		
treatment of disease		
alleviation of disease		
diagnosis of an injury or handicap		
monitoring of an injury or handicap		
treatment of an injury or handicap		
alleviation of an injury or handicap		
compensation for an injury or handicap		
investigation of the anatomy or a physiological process		
replacement of the anatomy or a physiological process		
modification of the anatomy or a physiological process		
control of conception		

with a medical device in order to enable the use to which the medical device is intended. [16, p. 6]

Accordingly, it is important for the manufacturer to define their product in detail, including any possible medical devices, accessories and their funtion, as well as the interfaces of the overall system. For example, medical devices can only be used within their intended purpose (vs. *off-label use* i.e. use against the manufacturer's instructions), but accessories can function as accessories to numerous different medical devices as long as their performance within these applications has been appropriately validated.

The accessories the manufacturer defines for their medical device(s) may or may not be a result of their own production. Aoccordingly, accessories acquired off-the-shelf (e.g. standard ECG measurement electrodes) are naturally not subjected to the design and development processes of the manufacturer themselves. Nevertheless, as the manufacturer is responsible for their product as an entity, they are required to prove the applicability of the used accessories via validation and to determine processes (e.g. supplier control) to maintain the applicability. For example, the manufacturer needs to guarantee the availability of the accessories for a certain period of time (e.g. lifetime of their device) and of the information concerning any possible product changes by their manufacturer. [20]

Other possible product categories whose treatment differs from that of an actual medical device, but which are regulated by the MDD include custom-made devices and devices intended for clinical investigations. The former is defined as a prod-

uct intended to the sole use of a particular patient and is, accordingly, specifically made for that person by the request of and according to the prescription by a qualified medical practitioner or other authorized person. The latter covers any devices intended to be used in investigations by a qualified medical practitioner or other authorized person, as defined in the MDD (Annex X). [16, p. 6]

After the different components of the product have been qualified they are classified based on the classification criteria and according to the eighteen different rules for classification defined in the MDD. Devices that fulfil the criteria for more than one risk class are always classified according to the highest one [7]. Additionally, in a case the view of the manufacturer is in conflict with that of the NB, a statement from the CA (e.g. Valvira) for whom the NB is a subject can be requested in order to resolve the dispute. [16]

Even though a device risk class can be determined wrongly for many reasons, due to human error or misapprehension, for example, some manufacturers classify their products in a higher risk class than required in purpose. The reason behind this overclassification is often to gain additional material to prove the device validity prior to entering markets outside the EU. [20][21] For example, within the US medical devices are divided into three separate risk classes: Class I, Class II, combining the European classes IIa and IIb, and Class III. Furthermore, the classification criteria differ from those mentioned in the MDD thus, possibly changing the risk class of the product when entering the US market. As the risk class only seldom changes downwards, the US authorities are likely to require substantially more comprehensive clinical evaluation and evidence before the product gets a market approval within the US, which complicates the manufacturer's activities also in the EU. [21]

As in the definition of the medical device, the manufacturer should aim to document the reasoning behind their device classification. The documentation can be done in a table form as in defining the product category, or rule by rule as described in Fig. 3.2. [28] Accordingly, surgically invasive devices intended for short-time use (i.e. continuous use of 1 hour to maximum of 30 days [16, p. 52]) generally fall within the Class IIa. However, if they fulfil one of the other functions mentioned in the Fig. 3.2, such as use in direct contact with central nervous system, they are classified accordingly, in Class III or in other applicable.

Even though most product features are well represented in the medical device qualification and classification rules, and some rules are even specifically drafted for particular devices (e.g. blood bags [16, p. 56]), there are products whose qualification and classification is not as straightforward as of those clearly fulfilling the relevant definitions. Accordingly, software used in medical applications is hard to define and classify due to its abstract nature compared to that of actual apparatuses and equipment. Because of this, the MDD addresses software used in medical

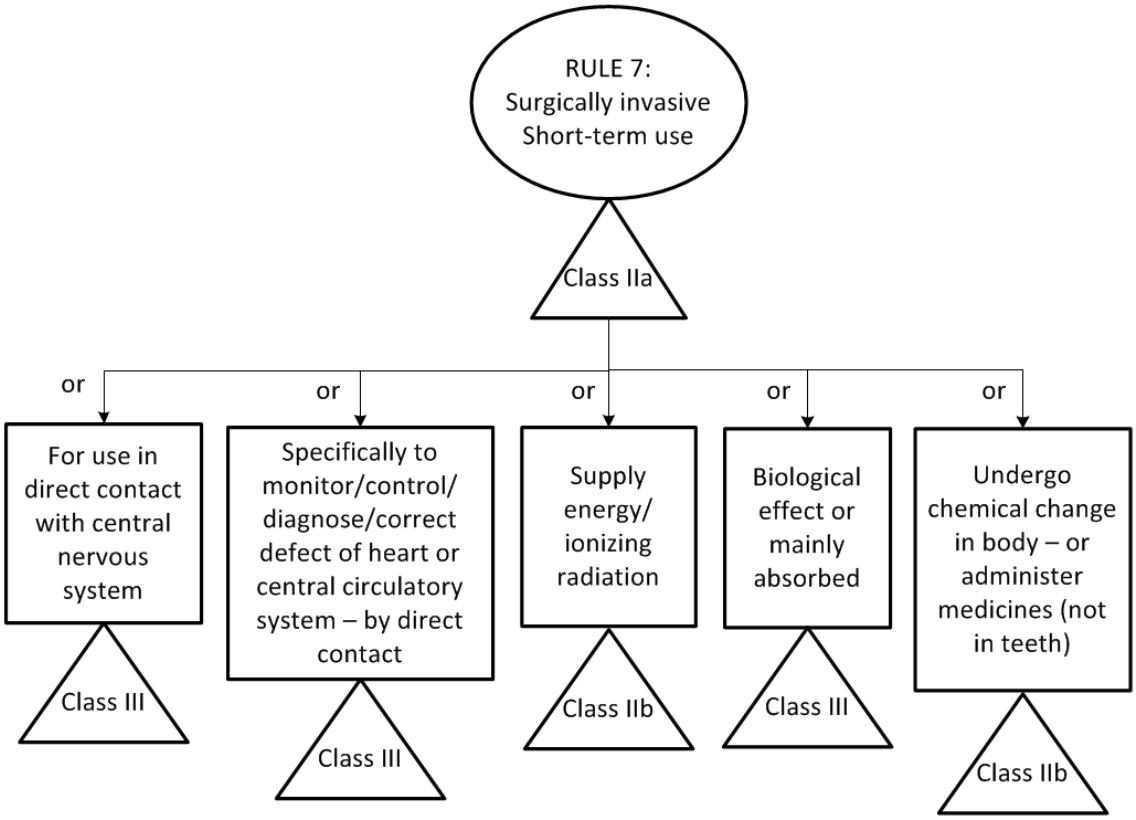

Figure 3.2: An example of classification of medical devices according to the Rule 7 (modified from [7, p. 19]).

applications separately. [16]

Standalone (medical) software is defined as software that is not incorporated in a medical device when it is placed on a market or made otherwise available [9, p. 6], and is thus, treated as a device in its own right. However, to be qualified as a medical device it must have a medical purpose as defined in the MDD and by the manufacturer in the intended purpose of the software. Accordingly, standalone software can be used for a variety of medical purposes, such as to control an apparatus, to provide information for immediate decision making and to provide diagnostic support for medical professionals. Standalone software that does not meet the definition of a medical device can still be used as an accessory for one and does, respectively, fall under the scope of the MDD (or the IVDMDD). [9, pp. 6-8]

To clarify the qualification and classification of medical software, the MDD dictates unambiguously that standalone medical software is always qualified as an active medical device [16, p. 52]. In addition, there are only four different classification rules addressing active devices and thus, applicable to the software: Rules 9, 10, 11 and 12. [9, p. 15]

As a difference to standalone software, software that is merely intended to drive a

medical device or influence its use i.e. embedded software, falls automatically under the same risk class as the device it is incorporated in and must be designed and manufactured accordingly. [9, p. 15]

3.2.3 Regulation and Requirements

After defining the intended purpose of the device and its risk class, the manufacturer is required to determine all relevant regulation the device and the manufacturer's processes need to fulfil to ensure and maintain the safety and performance of the product. Such regulation includes all relevant European directives and related requirements, as well as hENs to provide guidance on the implementation of these requirements. Additionally, the manufacturer has to define and document the requirements specific for their particular product (e.g. customer requirements) according to the intended purpose and overall device design. [8][30] For example, the customer may require that the device is of a specific colour or that a given standalone medical software will run on all available operating systems both of which constrain the product design.

Directives and Essential Requirements

A medical device manufacturer must decide between the fundamental directives, i.e. MDD, AIMDD and IVDMDD, in the very beginning of the design process of their product. The directive provides essential requirements for related devices based on the safety of the patient, users (if other than the patient) and of a third party, against which the final product is inspected by the NB in the end of its design and development process and prior to its market release. [20]

The manufacturer has to define all individual essential requirements applicable to their product, and to be able to prove their fulfilment within the final design by related design documentation, test plans and test results. If a requirement is found non-applicable, the manufacturer is expected to justify that decision.

An NB usually begins their audit with going through the definition of the essential requirements for particular device and the evidence on their fulfilment. Accordingly, the determination of the applicable and not applicable requirements and related justification should be documented. The document should also include references to any relevant design and development documentation to indicate how a particular requirement has been fulfilled and its fulfilment tested, when applicable. [20] The essential requirements are often documented in an Essential Requirements Check List as in that shown in Table 3.2.

It is mostly sufficient for the manufacturer to employ the appropriate medical device directive and hENs relevant for the product design and development. However,

Table 3.2: MDD essential requirements checklist [1].

Requirement: 10. Devices with a measuring function	**A/NA**	**Applicable standards or other applied processes**	**Reason for non-compliance**
10.1 Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.			
10.2 The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.			
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC.			

they should be aware of other European directives in addition to those mentioned. These directives rather address certain product features (e.g. energy sources and electromagnetic compatibility) than medical devices in particular, but medical devices may be covered by the scope of certain directives which may thus, require special attention. [8][20]

For example, the most recent change in medical device design and development within the EU was the implementation of the directive 2011/65/EU (Restriction of Hazardous Substances (RoHS) II). The directive addresses the use of certain hazardous substances, such as lead and mercury, in electrical and electronic equipment by dictating their maximum concentration as an allowed percentage by weight within homogeneous matter. The preceding version of the RoHS II, i.e. RoHS directive 2002/95/EU, did not include medical devices which are, however, included in the scope of the newest version essentially affecting the related processes. Accordingly, from 22.7.2014 forward all medical devices to be placed on the European market and falling under the scope of the RoHS II have to fulfil the related requirements. [18][35]

If found applicable, the medical device manufacturer has to prove the compliance of their product with RoHS II by self-declaring the adequacy of their design and development processes, compiling the related technical documentation, drawing up the EC DoC and finally, by affixing the CE marking. Nevertheless, the NB has neither responsibility nor right to challenge the alleged compliance. Within Finland, the compliance with the directive is generally supervised by the Finnish Safety and Chemicals Agency (Tukes). Due to the specific nature of the design and development of medical devices, however, their conformity with the requirements, like all other activities related to medical device development, is supervised and monitored by Valvira. [18]

Product Specific Requirements

Specifying the wanted product features is an essential part of medical device design and development as it begins the overall process of producing a product that will eventually perform as intended within its intended use environment. Requirement specification is also an essential part of the quality management of a medical device manufacturer required, regulated and supervised by the authorities. The expected result of the process of requirements planning forms a documented and controlled basis for the product realization process that, respectively provides frames for medical device design verification and validation. Accordingly, depending on the nature of the solution the device requirement specification should include at least the following: customer requirements (i.e. what does the customer want), regulatory requirements (e.g. essential requirements), functional requirements, performance requirements and environmental requirements (e.g. recyclability), when applicable. [30]

In general, the requirement planning consists of separate sequential phases. In the beginning, the manufacturer has to define any relevant customer and regulatory requirements to provide initial frames for the device design i.e. what does the customer want and what constraints does the regulation provide. Secondly, the manufacturer compiles all these requirements together and transforms them into requirements for the overall system and sub-systems, e.g. software design, hardware design, mechanical design, and so on. Finally, the system level requirements and related sub-requirements are converted into requirements for the product architecture i.e. requirements concerning the individual components that form the final product (e.g. electricity, electronics, mechanics and software) to enable the actual description of the final design by detailed planning. For example, the final product specification should address such aspects of the device design as the interfaces of different functional units, material properties, schematics, test specifications and electrical safety. [30, pp. 26-33]

Part of detailed panning is the definition of the components used in the electronic design of the device. The components are chosen based on specific criteria determined by the manufacturer. For example, for the manufacturer to be able to provide maintenance for their product over its lifetime they need to be sure of the availability of any components critical to their design (e.g. components having especially low tolerances, particular potential amplifiers or microcontroller(s)). However, there are also components defined as critical by the regulatory authorities.

Critical components from the regulatory point of view are those, whose malfunction or change of features can endanger the health of the patient or the user. In general, critical components include Printed Circuit Boards (PCBs), safety switches and lithium batteries, batteries and charging circuits, for example. [35]

Critical components incorporated into a device have to be listed over the product safety testing and cannot be changed for another without updating the related documentation (test reports and certificates). However, medical device regulations do not include a specific definition for which components are to be considered as critical and which are not. Requirements for critical components may also differ between different market areas. Accordingly, as the practices of different testing laboratories often differ from each other, the manufacturer is encouraged only to use components that already have as extensive international recognition as possible. [35]

Critical components that are certificated can be used as such assuming that the component manufacturer provides the medical device manufacturer with the related certificates. However, if there is a component performing a critical function that does not have the related certificate, the device manufacturer has to conduct additional safety tests according to the component specific IEC standard. As a result, the manufacturer obtains a certificate (i.e. '*Tested in Application*') of the comformity of the component to the related requirements and can apply it to their product. A datasheet provided by the component manufacturer is naturally not considered as a certificate or otherwise sufficient evidence of the safety of the component within medical applications. [35]

The process within which the requirements are defined and executed is often called the *Design Controls*, even though it is rather referred to as 'design and development' within the EU legislation. The process is described in Fig. 3.3 using a simple waterfall model. Requirements for a medical device should be documented in detail. The general idea is that the requirement document should be sufficiently comprehensive for a professional to produce the device solely by referring to the document and without any external help. [30]

User needs i.e. user requirements describe the fundamental requirements (other than those related to legislation) for the use of a product and may originate from several different sources such as the customer, (end) user, patient (n.d. the cus-

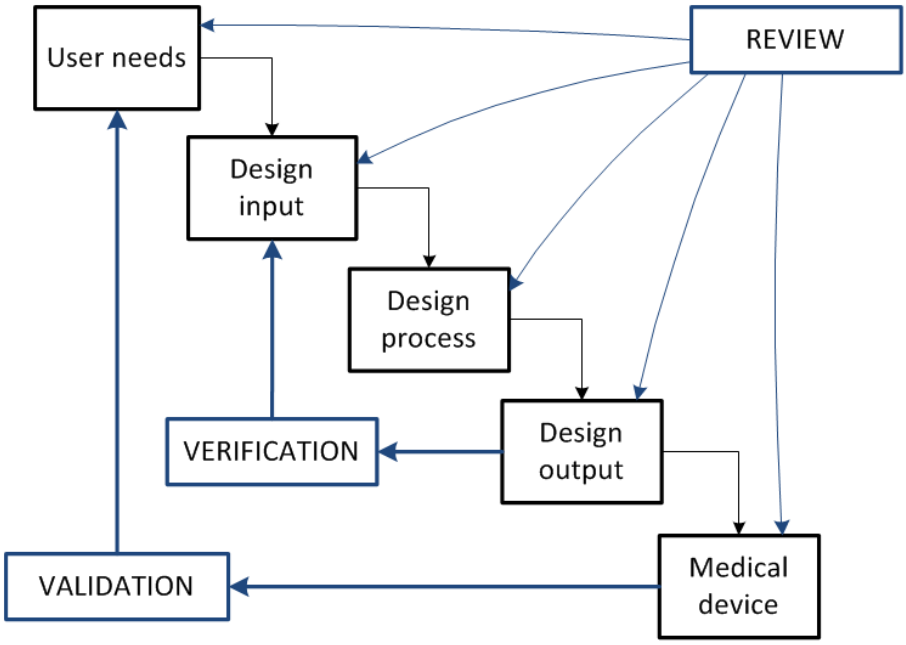

Figure 3.3: Design controls applied to a waterfall model (modified from [22, p. 3]).

tomer may also be the user and/or the patient and vice versa), engineer, designer, etc. Special attention should be paid to the definition of these requirements, as they specify the most essential features and possible restrictions for the device design. For example, neglecting the end user's view may result in a product design not applicable to its intended purpose, whereas by designing a product against the engineers recommendation the manufacturer may end up with a design impossible to execute. [22][30]

User requirements are often rather qualitative than quantitative and hence, need to be transformed into a measurable and more concrete form. For example, rather than defining the device as 'small', the manufacturer needs to provide the engineers with specific measurements of the PCB, of any holes in the device casing, of the device casing itself, etc. Quantitative requirements are then documented, transformed into *design and development inputs*, and finally, entered in the design process in a particular sequence producing related *design and development outputs*. Each output is verified via specified testing and their compliance with the input ensured respectively, after which the next input is inserted to the process. [22]

The tests related to the output verification must be designed beforehand and documented according to the manufacturer's instructions. In addition, the manufacturer must establish criteria for the approval of the related results according to which the assessment of the results is carried out. [30][35]

After the tests have been conducted, their results are to be documented respectively. The results must be easily obtainable, because of which the manufacturer is

encouraged to establish a system including the references from all relevant requirements to related test methods and their results. For example, the documentation can be done in table form, as shown in Table 3.3. [2] Accordingly, every individual requirement (i.e. requirement 7.1, 7.2, 7.3, etc.) connected to the temperature controller in question is further linked to a specific test method (i.e. test 7.1, 7.2, 7.3, etc.) determined and designed to verify that particular requirement. After every design input has been executed and related output(s) verified, a product prototype is manufactured and validated by testing it against its intended purpose and the related regulation. [2][22]

Table 3.3: An example of a traceability matrix for specific requirements and related testing [2].

Section	**Requirement**	**Test procedure**
7. Temperature controller	7.1	Test 7.1 Implementation of temperature controller
	7.2	Test 7.2 Temperature reading
	7.3	Test 7.3 Set temperature corresponds to got temperature
	7.4	Test 7.4 Temperature range
	7.5	Test 7.5 Temperature range over time
	7.6	Test 7.6 Temperature range over time higher precision
	7.7	Test 7.7 Temperature controller error messages

There is no fixed structure provided within the related regulation for a document listing the requirements for medical devices. Accordingly, the manufacturer may create their own documents and titles, as long as all the individual requirements can be found from the manufacturer's technical file and are traceable to the smallest detail from the initial document to a concrete device design and actual design implementation, including related verification activities and their documentation. However, there are certain more commonly known manners of documenting requirements for medical devices. [20][39]

User Requirements Specification (URS; sometimes established in two separate documents: Market Requirement Specification (MRS) and USR) is a document defining the customer and user requirements for the product. The exact content may vary between companies, but the document generally answers the question what is or needs to be done, presented in quantitative measures, when applicable. Following the establishment of the URS, the manufacturer produces a Technical Requirement Specification (TRS) that defines how the requirements determined in the URS are to be executed. The conformance of the individual product features

to the TRS is assessed by verification testing and the conformance of the product to the URS is evaluated at the end of product development via product validation. The relationship between the URS and the TRS and their role in the medical device development is presented in Fig. 3.4 using a so called V model of product development. [2]

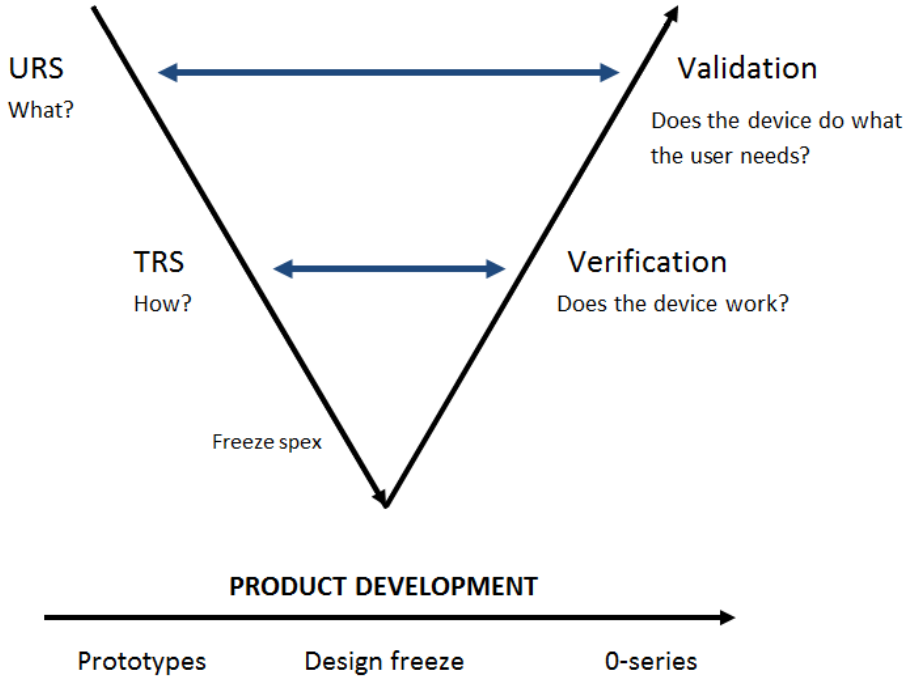

Figure 3.4: The URS and TRS incorporated into the process of product development [2].

Another way to define the appropriate requirements for the product is to compile a Market Requirement Document (MRD) accompanied by Functional Requirement Document (FRD) and Device Design Specification (DDS). Here, the MRD corresponds the URS, but is qualitative rather than quantitative and thus, suitable for a preparatory determination of requirements. Accordingly, in the MRD the manufacturer can define the size of their device as 'small' without taking a stand on the actual measurements. Quantitative FRD is prepared based on the definitions in the MRD, but still answers the question 'what is done'. Finally, the requirements become concrete in the DDS providing details about the actual execution of the device. [2]

Regardless of the form of documentation, the determined requirements are presented using the word *shall* [2]. For example, the manufacturer can define the size of a certain device as 'the device shall be of maximum 12 cm in length, 4 cm in width and 2 cm in depth'. The manufacturer can also provide directive sub-requirements further specifying the product features, such as 'the device should be less than 11.8 cm in length, 3.7 cm in width and 1.7 cm in depth'. However, even though the

use of the conditional verb *should* is not forbidden, it is frowned upon and its use should be avoided [30, p. 27]. Instead of using the conditional, the manufacturer is encouraged to provide a realistic tolerance to every quantitative requirement (e.g. 12 cm $\pm$ 0.2 cm) to increase the flexibility of the design and to decrease waste due to the potential instability and limitations of the manufacturing processes [2].

The adequacy and applicability of the user requirements, design inputs, design processes and outputs, as well as those of the verification and validation measures are inspected by the manufacturer over specified meetings called *design reviews*. The reviews are convened at particular stages of the process determined by the manufacturer and documented into their design and development documentation. As well as their progress and content, the people that have to be present in the review need to be determined in advance. In addition to the manufacturer and or their reprecentative, every design review should involve participants who have the relevant knowledge and expertise on, and are not personally involved in the matter at hand (e.g. particular design phase). [22]

After the requirement document has been approved by the review meeting, the manufacturer is obliged to provide devices that conform to the requirements and cannot sell products that differ from the given specifications. To change individual requirements, the manufacturer has to use a specified *change control* procedure which includes a formal assessment of the requirement and the proposed change, the evaluation of the effect of the change to other product features, its safety and performance, and its formal approval by signature(s) of an appropriate party, for example. [2][20]

Standards

Depending on the intended purpose of the device, its main functions and related requirements, the manufacturer is encouraged to search for any relevant standards applicable to the product or parts of it, to help defining the essential features of the device, such as the required level of safety and performance, and the processes required from the manufacturer. In addition, the manufacturer is adviced to seek for so called 'technical reports' published by the standardization bodies and addressing the implementation of particular standards. [20]

Unlike the EU legislation such as directives that are available for free, standards, being not legally binding, are subjects to a charge. They can be purchased via national standardization organizations and/or directly from the publishing party. Accordingly, the applicability of specific standards to particular products has to be defined carefully in each separate case. This evaluation is done based on the scope of the standard usually available for all, and often by interpreting the scope word by word. [20][41] For example, there are multiple standards for different medical devices

that *monitor* particular values or parameters that, even though may otherwise be widely applicable, do not address devices not having the monitoring feature.

Additionally, standards include so called *Normative References* to other standards that are either indispensable for the application of the related document, or otherwise recommended to be used together with that particular standard. When defined as indispensable, the manufacturer is to assume that the use of the particular standard without the ones mentioned as a normative reference is not sufficient to provide full compliance with the related requirements. Accordingly, the manufacturer has to study the scope of the other standards mentioned and decide whether they are or are not essential for the design and development of their medical device. [20]

Even though the EU only recognizes the hENs, other market areas may require other standards in addition, or other versions of the same ones. The manufacturer has to be aware of this from the very beginning if the product is intended to be sold also on markets outside the EU, because it increases the regulatory control and complicates the validation procedures the product needs to be subjected to. For example, a standard 60601-1 published by the IEC concerning medical electrical equipment has been amended for three times meaning that four different editions, 1.0, 2.0, 3.0 and 3.1, are currently available. The EU only recognizes the harmonized version of the standard, i.e. the third edition, as does the US FDA, but version 2.0 is still required by the Chinese regulatory authorities, for example. [36]

The manufacturer should be able to define all sections of different standards relevant to their device and justify, where appropriate, why some section are not applicable respectively. The manufacturer is encouraged to consult the authorities about the applicability, if found reasonable, and to purchase testing services from related providers, i.e. testing laboratories and Certification Bodies (CBs). A CB tests the device against any wanted standards and provides the manufacturer with a certificate of the compliance. [35] Even though the certificate is not required by the regulatory auhtorities, as long as the compliance is demonstrated in some other way, some specific customers (e.g. hospitals, private clinics, etc.) may require the certificate before they agree to purchase the device to themselves. [36]

Furthermore, the manufacturer can request for a pre-inspection from the chosen NB to get feedback on the readiness of their device and related processes, such as design and development and manufacturing. The service is subjected to a charge, as the formal overall inspection and the testing services provided by the CBs, but their use is highly recommended to facilitate the commercialization and to avoid any additional development costs caused by unnecessarily extensive redesign of the device. [35][36]

3.3 Assessment of Conformity

In order to assure the authorities that their product meets the essential requirements, the medical device manufacturer is required to conduct a *conformity assessment procedure* as instructed in the MDD. The directive provides more than one alternative from which the manufacturer is allowed to choose the one most appropriate for their product (and company). The applicability of the procedures is primarily constrained by the device risk class, but can also be affected by general policies of the manufacturing company i.e. their overall operational scope (e.g. primarily medical versus primarily other industry), product portfolio (e.g. the number of different medical devices or other products) and output (e.g. producing a single device at a time versus producing devices as mass production). [16][20]

3.3.1 Routes to Conformity

The possible routes to conformity depending on the device risk class are presented in Fig. 3.5. Accordingly, for the conformity assessment of Class I medical devices it is sufficient for the manufacturer to perform an internal assessment of the devices and the related technical documentation (Annex VII of the MDD). However, if the device is sterile or has a measuring function, the manufacturer has to conduct a more comprehensive assessment in addition to the DoC thus, selecting between three different assessment options. [16]

The conformity of Class Is and Im with the MDD is assessed via a process called EC verification (Annex IV), production quality assurance (Annex V), or product quality assurance (Annex VI) depending on the choice of the manufacturer. EC verification requires the involvement of an NB who verifies and certifies that the product conforms to its technical file i.e. technical documentation by inspecting every individual product, or each product batch, when applicable. [16] Accordingly, EC verification is rather utilized by companies producing a limited number of products (e.g. one magnetic resonance imaging machine per year or every six months) than those mass-producing smaller and simpler devices. [36]

Within the processes of production and product quality assurance, the NB assesses and monitors the manufacturer's quality system from parts specified in the MDD. Over the production quality assurance, the manufacturer is obliged to establish adequate processes for the manufacture of the product, whereas the product quality assurance addresses appropriate testing of the final device. Accordingly, the MDD requires that within the product quality assurance, the manufacturer examines each product or a representative sample of each batch and defines tests appropriate for the solution. Finally, the manufacturer self-declares that their product confirms with its technical file. [16]

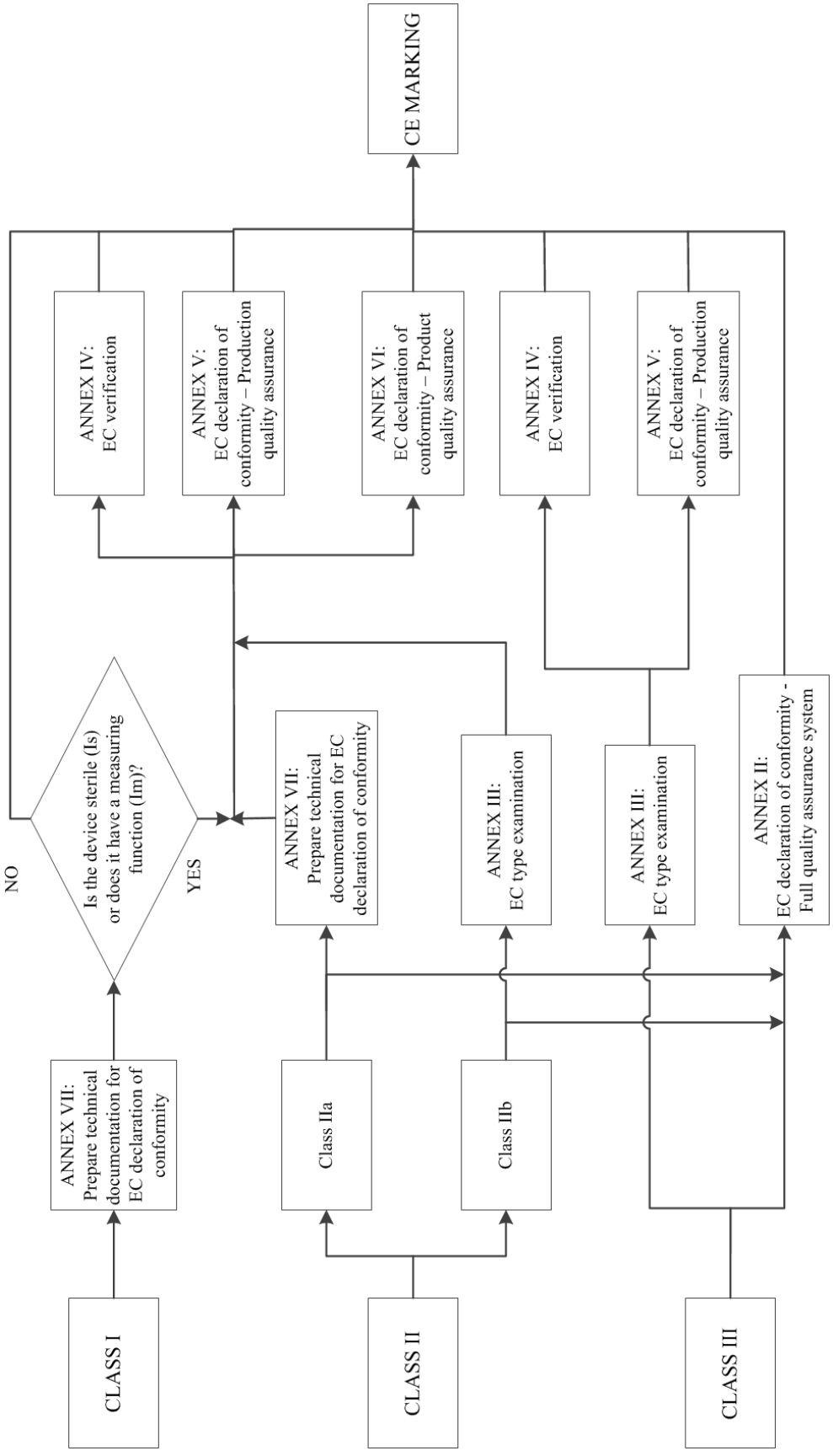

Figure 3.5: Possible routes for conformity assessment of medical devices depending on the device class [16].

The Class IIa medical devices can also be assessed via the processes mentioned above. However, Class IIa devices delivered in sterile state cannot be assessed via the product quality assurance, because the NB has to be able to ensure appropriate provision and maintenance of the sterile conditions within the manufacturer's production. [16]

Where found appropriate, the manufacturer can also produce a full QS for full quality assurance (Annex II) of Class IIa device. This is particularly popular within medical device manufacturers producing various different devices of different classification in mass production, as it increases the independence of the manufacturer, as well as their reliability and credibility amongst other actors within the same field of industry [20].

In this case, the manufacturer is required to establish a fully comprehensive Quality Management System (QMS) covering all aspects of their business including processes for the device design and development, subcontracting, manufacturing, etc. Accordingly, over their audit, the NB inspects the adequacy of the manufacturer's QS and the technical file of their product(s), and the manufacturer draws up the DoC as instructed in the MDD. [16]

Full quality assurance can also be applied to Class IIb and III medical devices. As an alternative to that, the manufacture of Class IIb products can conduct an EC type-examination in combination with the abovementioned processes of EC verification, production, or the product quality assurance, as that of Class III products only have the two former options. The EC type examination is a process through which the NB ascertains and certifies that a representative sample taken from the production of the manufacturer conforms to any relevant aspects of the MDD. Nevertheless, if the manufacturer produces sterile IIb devices they can only apply the solution consisting of type-examination and production quality assurance for the same reasons, as mentioned previously. [16]

Devices intended for clinical investigations and custom-made devices are managed separately from those mentioned above. Accordingly, the manufacturer of such devices is required to draw up a so called *Statement Concerning Devices for Special Purposes* (Annex VIII) based on the instruction within the MDD. [16]

Clinical Evaluation

Conformity assessment of medical devices includes a process of compiling clinical data also known as clinical evaluation of a medical device. Clinical data means the safety and/or performance related data that is generated over the use of a medical device. It can be obtained from clinical investigation(s) of the device concerned or from clinical investigation(s) or other studies of a similar device reported in scientific literature if the equivalence of the device to the one concerned can be demonstrated.

Clinical data may also include published and possibly unpublished reports on other clinical experience of either of the devices mentioned. [16, p. 7]

Clinical evaluation is the assessment and analysis of the clinical data concerning a medical device and a part of the conformity assessment of most medical devices. Basically, all medical devices need to be clinically evaluated to certain extent to ensure their adequate safety and performance as required by the authorities. Clinical evaluation is also an ongoing process that does not end when the CE marking is affixed, but lasts over the whole lifetime of the product. The manufacturer continuously collects use-related data on the clinical performance and safety of the device using it in their risk management activities and to further develop their products and processes. [6, p. 4]

Generally, in order to obtain sufficient amount of relevant clinical data all implantable devices and devices falling into the Class III have to go through an appropriate clinical investigation(s). Clinical investigation is a systematic investigation on humans conducted to assess the safety and performance of a medical device. Accordingly, the study is performed to verify the adequacy of the performance of the device under normal conditions of use and to determine any unwanted side-effects and the risk they constitute weighted against the intended performance of the device. [16, p. 57]

Quality Management of Medical Devices

Within the past decade, the focus in the assessment of medical device design and development has moved from testing individual devices to more and more comprehensive evaluation of the QMS of the medical device manufacturer. The evaluation covers both the assessment of the structure and general functionality of the QMS and the actual execution of the related processes based on the QMS documentation and requirements. Accordingly, in most market areas the compulsory type testing of medical devices has been partly, or entirely replaced by systematic quality management via appropriate verification and validation activities. [30, p. 11]

The MDD requires that a medical device manufacturer establishes adequate quality management procedures according to the chosen conformity assessment procedure and related requirements. Accordingly, the extend of the QMS is defined by the procedure and its adequacy evaluated over the related inspection. For example, if the manufacturer chooses to use the full quality assurance system they are required to establish an extensive selection of controlled and documented procedures covering the company in general i.e. their organizational structure and objectives and generally all activities that may affect the quality of the medical devices they produce. Additionally, the QMS also has to determine processes for the design and development of particular devices including their requirements planning, etc.

[20][16]

Creating a full QMS within medical device industry requires skills, expertise and resources. For example, it is estimated that for a small company entering the medical device market having no previous experience on the matter, it will require from six to twelve months of full-time work of around two employees to create a QMS appropriate for producing medical devices that conform to the relevant regulations and can thus, be actually placed on the EU market [20]. Fortunately, there are some widely used standardized guidance available on what such a QMS should include.

ISO has drawn up a standard on quality management of medical devices first published in 1996, based on standard ISO 9001 that addresses QMSs in general. Accordingly, the standard EN ISO 13485:2012 *Medical devices - Quality management systems - Requirements for regulatory purposes*, harmonized by the CEN in 2012 based on its international predecessor ISO 13485:2003, and related technical report CEN ISO TR 14969 on the implementation of the related requirements provide quite comprehensive and harmonized guidance on the relevant aspects of how to produce high-quality medical devices taking into account the regulatory requirements for the essential safety and performance, as well as the customer requirements of the product within different stages of their life cycle. [30, p. 11] The relationship of the EN ISO 13485 with the requirements for full quality assurance system defined in the MDD is discussed in the Annex ZB of the standard. Accordingly, there are some aspects in the MDD that are not covered by the standard and has thus, to be defined by the manufacturer in addition to the ones mentioned in EN ISO 13485 [22][39]

The standard indicates the issues the manufacturer needs to address and processes they need to develop, document, carry out, control and monitor without going into detail on how the activities are to be implemented. Instead, it is the GHTF who published guidance documents on the execution of an actual QMS and the development of related processes, respectively. [39][23]

Accordingly, the QMS consists of the definition of the management responsibilities including the determination of management commitment, customer focus, quality policy of the company and management review; resource management including the definition of the provision of resources, human resources (e.g. qualifications of the employees) and company infrastructure; and product realization including the definition of customer-related processes (e.g. customer communication), design and development of the product, and purchasing activities. Finally, the QMS has to address the after-sales measures by defining adequate processes for measurement, analysis and improvement including the definition of how to handle the internal and external feedback, to control nonconforming products and what measures should be taken for improvement (e.g. corrective and preventive actions). [39]

In addition to quality management, the manufacturer is obliged to establish appropriate risk management measures, as required in the MDD by either implementing a separate risk management system or by integrating the related processes into the QMS. Required risk management activities are described in a hEN EN ISO 14971 *Medical devices - Application of risk management to medical devices* (2012) and related guidance is provided in related documents published by the GHTF. The main difference between risk management within medical device industry and that of many other products is that, due to the vigorous control of their design and development, the risk management of medical devices rather focuses on the device itself aiming to control and maintain its safety and adequate performance accordingly, than on risks concerning the related business, for example. [39]

4. IMPEDANCE PNEUMOGRAPHY MEASURING SYSTEM: AN INITIAL PRODUCT DEFINITION FOR REGULATORY PURPOSES

The chapter summarizes the results of the Study. The results include the initial product definition for the IP measuring system for regulatory purposes i.e. the initial definition of its intended purpose, qualification and classification. Furthermore, the results discuss the directives and hENs applicable to the product, its feasibility and the initial MRD produced over the Study.

4.1 General

The IP measuring system (hereafter referred to as the Product) currently consists of a measuring device (hereafter referred to as the Device) and related articles, and computer software (hereafter referred to as the Analysis Software). The use of the Device requires four electrodes one pair of which is used to inject a current to the patient's thorax and another pair to measure the related response as a potential difference, i.e. a voltage, between them. The voltage is further converted into an impedance signal which is stored in the Device's memory. Additionally, the Device records the patient's ECG for signal processing purposes and activity data via acceleration sensor. The Device incorporates embedded software that controls its operations.

To function as intended the Device requires four electrodes (single-use surface electrodes) per measurement, related cables and connectors, a charger (assuming that the device has a rechargeable battery), related cables and connectors, and a shirt to be worn by the patient over the measurement. The shirt is used to secure the electrodes and the cables connecting them to the Devive and bears no clinical importance.

The data recorded by the Device is fed into the Analysis Software, which processes the data and provides a cleared bioimpedance signal. The Analysis Software displays the respiratory flow i.e. breathing of the patient and calculates certain related parameters for diagnostic purposes.

In most current applications used in asthma diagnostics, as well as in some applications technologically similar to the Product (e.g. portable ECG measuring system

continuously measuring the ECG signal for diagnostic purposes), it is common to use a symptom diary to record any changes in the patient's condition over the measurement. The diary is designed to provide additional information to support the related diagnostics made based on the measurement data. Usually, the symptom diary is filled up by the patient themselves (e.g. adult patients) or by their guardian(s) (e.g. children or challenged people as patients) including the times when the measurement began and ended, whether there were some particularly defined symptoms present over the measurement (e.g. shortness of breath), when the symptoms occurred, and so on. Accordingly, a symptom diary (hereafter referred to as the Diary) will most likely be provided by the manufaturer in addition to other articles related to the Product.

4.2 Intended Purpose and Qualification

Definition of the intended purpose of the Product and its different components affects essentially its qualification. Accordingly, two different interpretations of the intended purpose of the Device and its effect to the qualification of the Product are described within the next sections.

4.2.1 Device and the Analysis Software: An Accessory and a Medical Device

The following sections describe a situation where the Device is defined as an accessory to a medical device i.e. to the Analysis Software.

Device

The intended purpose of the Device within the IP application can be defined, as follows.

> "The Device is intended to be used with the Electrodes (four per measurement) and the Shirt by healthcare professionals or other appropriate party, e.g. the patient's guardian(s), in healthcare facilities or in home healthcare environment on infants and young children under the age of seven for a continuous several-hour (12-24) measurement of thoracic bioimpedance. The measurement is conducted over night while the patient is ideally asleep. Over the measurement, the patient should remain as still as possible.
>
> The Device obtains the bioimpedance signal by injecting a small current to the patient's thorax, measuring the resulting voltage and converting the current and voltage data into an impedance signal."

Based on the intended purpose of the Device, the Device is not a medical device by definition. The qualification is described in Table 4.1. Accordingly, the Device is defined as an accessory to the Analysis Software.

Table 4.1: Qualification of the Device as an individual product.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease		X
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

Analysis Software

The intended purpose of the Analysis Software is defined, as follows.

> "The Analysis Software is intended to be used by healthcare professionals in healthcare facilities for processing a thoracic bioimpedance signal measured and recorded by the Device, in order to provide information on the respiration and cardiac induced variations of the thoracic bioimpedance in signal form and in particular individual parameters to facilitate the diagnosis and management of asthma in infants and young children under the age of seven."

The Analysis Software is always a medical device by definition due to its use in diagnostics, as shown in Table 4.2. Furthermore, the Analysis Software is defined as standalone medical software and is thus, classified as an active medical device.

4.2.2 Device and the Analysis Software: Two Medical Devices

The following sections describe the situation if both the Device and the Analysis software are defined as medical devices thus, forming a medical system.

Table 4.2: Qualification of the Analysis Software.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease	X	
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

Device

The intended purpose of the Device within the IP application can be defined, as follows.

> "The Device is intended to be used with the Electrodes (four per measurement) and the Shirt by healthcare professionals or other appropriate party, e.g. the patient's guardian(s), in healthcare facilities or in home healthcare environment for infants and young children under the age of seven for a continuous several-hour (12-24) measurement of thoracic bioimpedance *in combination with the Analysis Software for the diagnosis and management of asthma.* The measurement is conducted over night while the patient is ideally asleep. Over the measurement, the patient should remain as still as possible.
>
> The Device obtains the bioimpedance signal by injecting a small current to the patient's thorax, measuring the resulting voltage and converting the current and voltage data into an impedance signal."

Accordingly, the Device can now be defined as a medical device. The qualification is described in Table 4.3.

Analysis Software

The intended purpose, as well as the qualification of the Analysis Software remains unchanged.

Table 4.3: Qualification of the Device as a part of a diagnostic system.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease	X	
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

4.2.3 Diary

The intended purpose of the Diary is defined, as follows.

> "The Diary is intended to be used by healthcare professionals as a supportive document for the diagnosis of asthma in infants and young children under the age of seven together with the data provided by the Analysis Software."

The Diary, as an individual product, is intended to provide data that is assumed to have clinical relevance to the diagnostics of asthma. Accordingly, the Diary is defined as a medical device, as described in Table 4.4.

4.2.4 Electrodes and the Shirt

In order for the Device to perform as intended it requires two sets of different accessories, as already described in its intended purpose: a set of four measurement electrodes per measurement (hereafter referred to as the Electrode(s)) to inject current and measure voltages, and a shirt (hereafter referred to as the Shirt) to secure the Electrodes and related cables. The following sections discuss the different possibilities of obtaining the mentioned accessories and the effect of the chosen solution on the manufacturer.

Table 4.4: Qualification of the Diary as a diagnostic instrument.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease	X	
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

Electrodes

The Electrodes used in the IP measurement are surface electrodes (non-invasive) intended for single-use only i.e. disposable electrodes. If the Electrodes are bought off-the-self, it is sufficient for the manufacturer to validate them for the related measurement as an accessory to the Device. However, if the Electrodes are defined as a product of the manufacturer and purchased as custom made they have to be qualified as accessories to the Device, as well as designed and developed within the QMS of the manufacturer.

Accordingly, the intended purpose of the set of Electrodes would be, as follows.

> "The Electrodes are intended to conduct current to a human body and to sense voltages on the body surface."

According to their intended purpose, the Electrodes are not qualified as a medical device, as such, as described in Table 4.5

Shirt

The shirt shall be custom made for the manufacturer due to specific customer requirements and requirements concerning its usability and applicability. If the use of the Shirt as an accessory to the Device is referred to in the intended purpose defined for the Device (as within this Study), the manufacturer has to define the Shirt as an accessory to the Device and control the related processes as described within their QMS. Accordingly, not using the Shirt over the IP measurement for whatever

Table 4.5: Qualification of the Electrode as an individual product.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease		X
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

reason (e.g. allergies) would be *off-label use* i.e. use against the manufacturer's instructions. Even though this would remove the responsibility of the manufacturer and thus, not affect their activities, it can restrict the overall use of the Product in its intended purpose (e.g. exclude patients not able to wear the Shirt) and should hence, be considered thoroughly before making any final qualifications.

Accordingly, if defined as an accessory to the Device, the intended purpose of the Shirt in general would be, as follows.

> "The Shirt is intended to be worn over a measurement which includes the use of surface electrodes on the upper body of the patient to help to secure the electrode-skin connection and the cables related to the electrodes, to an appropriate extend."

According to the intended purpose, the Shirt is not defined as a medical device, as shown in Table 4.6

4.3 Classification

The following sections address the classification of the Device, the Analysis Software and the Diary, as well as the Electrodes and the Shirt defined as products of the manufacturer and accessories to the Device.

Table 4.6: Qualification of the Shirt as an individual product.

Definition: *... intended by the manufacturer to be used for human beings for the purposes of:*	**A**	**NA**
diagnosis of disease		X
prevention of disease		X
monitoring of disease		X
treatment of disease		X
alleviation of disease		X
diagnosis of an injury or handicap		X
monitoring of an injury or handicap		X
treatment of an injury or handicap		X
alleviation of an injury or handicap		X
compensation for an injury or handicap		X
investigation of the anatomy or a physiological process		X
replacement of the anatomy or a physiological process		X
modification of the anatomy or a physiological process		X
control of conception		X

4.3.1 Device

Whether the Device is qualified as an accessory or a medical device, it is classified and developed as a medical device of its own right. Accordingly, it is an active device falling to the Class IIa according to the classification Rule 10, as described in Table 4.7. The embedded software incorporated into the Device falls into the Class IIa, respectively.

4.3.2 Analysis Software

The Analysis Software is classified as an active medical device and falls into the Class IIa according to the classification Rule 10, as described in Table 4.8.

4.3.3 Diary

The Diary is a non-invasive device and classified according to the classification Rule 1, as shown in Table 4.9. Accordingly, the Diary falls into the Class I.

4.3.4 Electrodes

The Electrodes are non-invasive and classified according to the classification Rule 1, as shown in Table 4.10. Accordingly, the Electrodes fall into the Class I.

Table 4.7: Classification of the Device and related embedded software.

Classification rules for active devices:	**Class:**	**A**	**NA**
(Rule 9:) Active therapeutic devices intended to administer or exchange energy	IIa		X
(Rule 9:) Active therapeutic devices intended to administer or exchange energy in potentially hazardous way	IIb		X
(Rule 9:) Active therapeutic devices intended to control or monitor or influence directly the performance of a Class IIb active therapeutic device	IIb		X
(Rule 10:) Active device *for diagnosis intended to supply energy*, to image In Vivo distribution of pharmaceuticals, or for direct diagnosis or monitoring of vital physiological processes	IIa	X	
(Rule 10:) Active device for diagnosis specifically intended to monitor vital physiological parameters where variations could result in immediate danger	IIb		X
(Rule 10:) All devices emitting ionizing radiation and intended for diagnostic and therapeutic interventional radiology	IIb		X
(Rule 11:) Active devices to administer or remove medicines and other substances to or from the body	IIa		X
(Rule 11:) Active devices to administer or remove medicines and other substances to or from the body in potentially hazardous way	IIb		X
(Rule 12:) All other active devices	I		X

4.3.5 Shirt

The Shirt is non-invasive device and classified according to the classification Rule 1, as shown in Table 4.11. Accordingly, the Shirt falls into the Class I.

4.4 Applicable Directives and Standards

EU directives applicable to the Product are listed in Table 4.12. Accordingly, hENs applicable to the Product are listed in Tables 4.13, 4.14 and 4.13 according to whether they address the general principles in medical device manufacturing and marketing, the manufacturer's processes, or specific features of the Product. The standards addressing the development of the Diary, the Electrodes and the Shirt are not addressed within this Study, in particular.

4.5 Feasibility Study

Feasibility of the Product was investigated and documented accordingly in a Feasibility Study document. The document discusses the overall product concept (offered products/product components and services, e.g. the initial product definition), tech-

Table 4.8: Classification of the Analysis Software.

Classification rules for active devices:	**Class:**	**A**	**NA**
(Rule 9:) Active therapeutic devices intended to administer or exchange energy	IIa		X
(Rule 9:) Active therapeutic devices intended to administer or exchange energy in potentially hazaedous way	IIb		X
(Rule 9:) Active therapeutic devices intended to control or monitor or influence directily the performance of a Class IIb active therapeutic device	IIb		X
(Rule 10:) Active device for diagnosis intended to supply energy, to image In Vivo distribution of pharmaceuticals, or *for direct diagnosis* or monitoring *of vital physiological processes*	IIa	X	
(Rule 10:) Active device for diagnosis specifically intended to monitor vital physiological parameters where variations could result in immediate danger	IIb		X
(Rule 10:) All devices emitting ionizing radiation and intended for diagnostic and therapeutic interventional radiology	IIb		X
(Rule 11:) Active devices to administer or remove medicines and other substances to or from the body	IIa		X
(Rule 11:) Active devices to administer or remove medicines and other substances to or from the body in potentially hazardous way	IIb		X
(Rule 12:) All other active devices	I		X

Table 4.9: Classification of the Diary.

Classification rules for non-invasive devices:	**Class:**	**A**	**NA**
(Rule 1:) Devices that *do not touch the patient* or contact only intact skin	I	X	
(Rule 2:) Devices intended for channelling or storing blood, other body fluids, organs, parts of organs or tissues for eventual administration	IIa		X
(Rule 2:) Devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for eventual administration that can be connected to an active medical device in Class IIa or higher	IIa		X
(Rule 2:) Other devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body	I		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids intended for infusion	IIb		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids by filtration, centrifugation, or exchange of gas or heat	IIa		X
(Rule 4:) Devices intended to be in contact with injured skin as a mechanical barrier, for compression, or for absorbtion of exudates	I		X
(Rule 4:) Devices intended to be in contact with injured skin: for wounds which breach dermis and heal only by secondary intent	IIb		X
(Rule 4:) Other devices intended to be in contact with injured skin, including devices intended to manage the microenvironment of a wound	IIa		X

Table 4.10: Classification of the Electrodes.

Classification rules for non-invasive devices:	**Class:**	**A**	**NA**
(Rule 1:) Devices that do not touch the patient or *contact only intact skin*	I	X	
(Rule 2:) Devices intended for channelling or storing blood, other body fluids, organs, parts of organs or tissues for eventual administration	IIa		X
(Rule 2:) Devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for eventual administration that can be connected to an active medical device in Class IIa or higher	IIa		X
(Rule 2:) Other devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body	I		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids intended for infusion	IIb		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids by filtration, centrifugation, or exchange of gas or heat	IIa		X
(Rule 4:) Devices intended to be in contact with injured skin as a mechanical barrier, for compression, or for absorbtion of exudates	I		X
(Rule 4:) Devices intended to be in contact with injured skin: for wounds which breach dermis and heal only by secondary intent	IIb		X
(Rule 4:) Other devices intended to be in contact with injured skin, including devices intended to manage the microenvironment of a wound	IIa		X

Table 4.11: Classification of the Shirt.

Classification rules for non-invasive devices:	**Class:**	**A**	**NA**
(Rule 1:) Devices that do not touch the patient or *contact only intact skin*	I	X	
(Rule 2:) Devices intended for channelling or storing blood, other body fluids, organs, parts of organs or tissues for eventual administration	IIa		X
(Rule 2:) Devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for eventual administration that can be connected to an active medical device in Class IIa or higher	IIa		X
(Rule 2:) Other devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body	I		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids intended for infusion	IIb		X
(Rule 3:) Devices intended to modify biological or chemical composition of blood, body liquids, or other liquids by filtration, centrifugation, or exchange of gas or heat	IIa		X
(Rule 4:) Devices intended to be in contact with injured skin as a mechanical barrier, for compression, or for absorbtion of exudates	I		X
(Rule 4:) Devices intended to be in contact with injured skin: for wounds which breach dermis and heal only by secondary intent	IIb		X
(Rule 4:) Other devices intended to be in contact with injured skin, including devices intended to manage the microenvironment of a wound	IIa		X

Table 4.12: Directives applicable to the design and development of the Product.

Directive:	**Description:**
93/42/EEC	Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
2007/47/EC	Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market
1999/5/EC	Directive 1999/5/EC of the European Parliament and of the Council of 9 March 1999 on radio equipment and telecommunications terminal equipment and the mutual recognition of their conformity
2011/65/EC	Directive 2011/65/EC of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment
2004/108/EC	Directive 2004/108/EC of the European Parliament and of the Council of 15 December 2004 on the approximation of the laws of the Member States relating to electromagnetic compatibility and repealing Directive 89/336/EEC

Table 4.13: hENs applicable to the manufacturing and marketing of medical devices in general.

Standard:	**Description:**
EN 1041:2008	Information provided by the manufacturer of medical devices.
EN ISO 10993-1:2009	Biological evaluation of medical devices - Part 1: Evaluation and testing.
EN ISO 14155:2011	Clinical investigation of medical devices for human subjects. Good clinical practice.
EN ISO 15223-1:2012	Medical devices. Symbols to be used with medical device labels, labelling and information to be supplied.

Table 4.14: hENs applicable to specific processes of a medical device manufacturer.

Standard:	**Description:**
EN ISO 13485:2012	Medical devices. Quality management systems. Requirements for regulatory purposes.
EN ISO 14971:2012	Medical devices. Application of risk management to medical devices.
EN 62366:2008	Medical devices. Application of usability engineering to medical devices.

Table 4.15: hENs applicable to specific features of the Product.

Standard:	**Description:**	**Product component:**
EN 60529/ A1:2000	Degrees of protection provided by enclosures (IP code)	The Device
EN 60601-1:2006/ AC:2010	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance.	The Device
EN 60601-1-2:2007/ AC:2010	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests.	The Device
EN 60601-1-6:2007/ AC:2010	Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	The Device
EN 60601-1-11:2010/ AC:2010	Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment	The Device
EN 60950-1:2005/ AC:2011	Information technology equipment. Safety - Part 1: General requirements.	The Device, the Analysis Software
EN 62304:2006/ AC:2008	Medical device software. Software life-cycle processes.	The Analysis Software

nology considerations (i.e. initial analysis of the product specific requirements), design constraints (e.g. physical constraints and regulation), intended product market place, marketing strategy of the becoming company, related schedule, financial projections, potential risks (initial analysis), and findings and recommendations based on the overall study. As an example of the content of the feasibility study, the initial workflow of the Product, i.e. current understanding on how the Product will be used, is illustrated in Fig. A.1 and described in words in Appendix A. Different possible product solutions for the realization of the workflow are described in Appendix B, respectively.

The document is not intended to be used for regulatory purposes as such, but to provide initial guidelines for further development of the Product.

4.6 Market Requirement Document

A tentative MRD was created based on the considerations made over the individual Feasibility Study meetings. The document consists of six separate requirement categories: general requirements, system level requirements, requirements for the Device, accessories (e.g. the Electrodes, the Shirt), embedded software requirements, and requirements for the Analysis Software. The document is not intended to be used for regulatory purposes as such, but to provide an initial framework of requirements for the design and development of the final Product.

5. DISCUSSION

The chapter discusses the adequacy and applicability of the results of the Study. Also, the latter sections of the chapter summarize the applicability of the results to medical device design in the future, including a brief discussion on becoming changes in related regulation.

5.1 General

As described in this Study, there are no fixed guidelines for the implementation of the EU regulations concerning medical device design and development. Even though the flexible nature of EU legislation is often seen as a strength of the EU allowing the manufacturer to use their own expertise and self-defined processes, it can cause a lot of pressure and inconvenience to smaller companies entering the medical device markets for the first time. The establishment of adequate processes for quality and risk management, for control and related documentation is burdensome and requires experience and resources almost invariably forcing smaller manufacturers to lean on external help.

5.2 Impedance Pneumography Measuring System: An Initial Product Definition for Regulatory Purposes

The design and development, and the manufacturing processes of the current solution of the Product do not fulfil the regulatory requirements for those of medical devices. Accordingly, there is no organized documentation on the processes, the related decision making, their results, software design process, and so on. In addition, no change control has conducted because of which the effects of any previously made modifications are unknown and not justified in any adequate manner of documentation.

Due to the lack of process control, the current solution cannot be sold within the EU and the Product has to be redesigned. In reality this means that before they are able to sell the product, the manufacturer has to first establish any required processes and then design, develop and manufacture the product as a new medical device. The manufacturer also has to create appropriate control and maintenance procedures for related activities required by the regulatory authorities (e.g. procedures for

purchasing, document control and risk management).

Defining the Product proved to be more difficult than anticipated due to the lack of original documentation about the development of the Product, and of published instructions on how to develop an appropriate product definition. As mentioned previously, the related directives and standards provide a very comprehensive idea on what is required from the manufacturer of medical devices, but there is only a little public information available on how to actually execute the objectives of the regulation. Accordingly, participating the seminars and informative lectures provided by and actively contacting the organizations and authorities operating within the medical device industry (e.g. Valvira, FiHTA and NBs), as well as networking is highly recommended. Information and connections gained from such seminars proved to be vital for the completion of this Study.

However, due to some physical constraints, such as lack of resources (e.g. time and specialist manpower), the product definition provided by the Study cannot be considered as final or applicable to the regulatory design and development process of the Product. Accordingly, it is intended to be used as a directive document for future needs and in future activities.

5.2.1 Intended Purpose, Qualification and Classification

The intended purpose of the Product was initially defined for the overall system based on the definition of a medical electrical system (includes both hardware, e.g. measurement electronics, and software). Accordingly, the initial definition of the intended purpose was similar to that described below.

> ”The Product is intended to be used to measure and analyze the respiration and cardiac induced variations of thoracic bioimpedance to facilitate the diagnosis and management of childhood asthma.”

It was soon realized, however, that the definition was not sufficiently detailed for regulatory purposes because the functions of the Device and the Analysis Software differ so essentially from each other. Accordingly, the intended purpose of the Device was defined separately from that of the Analysis Software.

Device and the Analysis Software

In general, it was relatively straightforward to define the intended purpose of the Device, as all its essential functions were already quite comprehensively determined. However, whether or not the intended purpose should include a reference to the measurement of the single channel ECG was not as easy to determine. For now, based on the Study and current medical device regulation it is recommended that the

ECG measurement is not mentioned as an intended activity of the Device, because no clinically significant data on the cardiac activity of the patient is provided based on the measurement, and no ECG signal is displayed by the Analysis Software.

However, it is essential that the issue of whether or not the define the ECG measurement as a part of the intended purpose of the Device or not is discussed and resolved within the formal design and development process. If the ECG measurement is left out against the regulation, the Device cannot be legally commercialized. On the other hand, if it is unnecessarily mentioned within the definition of the intended purpose, the Device has to be validated also for the ECG measurement increasing the related requirements and testing including more than one additional applicable hEN.

The Device also measures acceleration data using a single three-dimensional acceleration sensor. However, the diagnostic relevancy of the positional and activity data obtained as a result is yet to be defined, because in reality the motion artefact caused by movement (e.g. using the bathroom and 'tossing and turning') over the measurement is so much larger in magnitude than the bioimpedance signal that those signal sections can be discovered visually and have to be removed. Nevertheless, if the acceleration sensor is included to the final design of the Device, the related data will most probably be displayed by the Analysis Software in parallel with the impedance signal for diagnostic purposes. In this case, the measurement of the acceleration data would have to be included to the definition of the intended purpose of the Device.

The target population of the Device and the Analysis Software is currently defined as infants and young children under the age of seven, because there are currently no other reliable methods for the diagnosis of childhood asthma within the age group. However, as the performance of medical devices has to be validated according to their intended purpose, the definition of 'infants and young children' should be discussed further within the formal design and development process. As implicated by the current definition, it should be possible to assume that the Device measures the bioimpedance as intended from all children regardless of their size, shape and race, for example. Accordingly, even though it can be assumed to be fairly insignificant, the risk of the Device not functioning as expected in every individual within the target population and its effects should be assessed within the becoming risk management process of the manufacturer.

The definition of the intended purpose of the Analysis Software was quite straightforward, respectively. However, after defining the intended purposes of both of the two product components, it was soon realized that the Device and the Analysis Software do not have to be commercialized as a system, but can also be designed, manufactured and CE marked as individual devices. Furthermore, it was discovered

that as an individual product having no formal connection to the Analysis Software, the Device is not actually a medical device by its definition: it cannot be used for diagnosis, treatment, alleviation, or any other clinical purposes without additional equipment. Accordingly, the Analysis Software was determined as a medical device and the Device as an accessory to the Analysis Software. Regardless of this qualification, however, the Device has to be commercialized as a medical device of its own right as defined in the MDD. This includes the affixing of the CE marking prior its market release separately from the Analysis Software.

Defining the Device as an accessory has multiple advantages compared to handling the two components together as a medical system. For example, as an accessory the Device can be used as an accessory also to medical devices other than the Analysis Software. This becomes essential if the manufacturer decides to extend their product portfolio by establishing new medical devices and applications. Also, as an accessory the Device can be developed separately from the Analysis Software. They need to be proved applicable to each other, and if changes are made to the final Device design the effects of the changes to the performance of the Analysis Software have to be assessed. However, if no significant effects are discovered, no additional actions have to be taken.

Diary

The definition of the intended purpose, the qualification and classification of the Diary did not require a lot of additional work even though it was found somewhat surprising to qualify a 'piece of paper' as a medical device. Accordingly, belonging to the risk Class I, the Diary has to be designed, developed and validated, accordingly. However, the related processes are sufficiently light to determine and execute, and inexpensive respectively, as the conformity of the Diary with the related requirements can be self-declared by the manufacturer.

If more convenient for the manufacturer and the healthcare professionals, a solution already available could be used where possible and if commonly available for all users. However, a validation i.e. clinical evaluation has most likely to be conducted to ensure the applicability of the used diary to the Product. A reference to past use of similar 'devices' and a statement from a clinician or other appropritate party on symptoms related to asthma are probably more than sufficient to prove the required compliance, as such tools are already widely in use and the most common symptoms of asthma quite well known within medical professionals.

Accessories to the Device

In order for the Device to perform as intended it requires certain additional articles. The Device is rechargeable, because of which a charger and related cables are required. However, the mentioned articles shall not be produced by the manufacturer (i.e. they are most likely bought off-the-self). Also, as they have no clinical significance they do not, naturally, have to be medical devices by their definition. However, there are certain other requirements for electronic equipment used in healthcare facilities to be considered, because they may sometimes cause interference coupling to other devices used in the same space. The manufacturer has to ensure that the articles provided along with the Device fulfil these requirements and are safe to be used within hospital environment, for example.

The Electrodes used in the IP measurement on children have to or should be intended for paediatric use. In addition, they should not be intended to any other particular application (if not bioimpedance measurement), such as the ECG, but rather for 'general purpose' and specifically to inject current and sense voltages. As the matter has not yet been discussed further, standard ECG electrodes are currently used instead.

If the manufacturer wants to provide their own electrodes especially intended to be used with the Device and within the IP measurement application, they are most likely to be required to become also the legal manufacturer of these electrodes. On the other hand, if bought off-the-shelf, the manufacturer only has to verify the use of the electrodes in the IP measurement application and provide the authorities with the related test results to prove that the electrodes do not impair the performance of the Device. [39][40]

If the Shirt is not defined as an accessory to the Device, but as an article recommended to be used over the measurement, it does not have to fulfil the requirements for medical devices as it has no clinical significance. However, if defined as an accessory, it has to be developed under the QMS of the manufacturer, as defined in the MDD.

As created specifically based on the manufacturer's request and specifications, comprehensive requirements for the Shirt need to be determined. Accordingly, the activities and processes of the related supplier have to be monitored and controlled effectively to ensure the conformity of the Shirt with the related specifications. The manufacturer needs to be informed of any changes in the supplier's processes to be able to assess the changes within their own risk management practices. Accordingly, if the change is found insignificant, the manufacturer shall most probably continue using the same supplier, but if found to impair the basic safety or essential performance of the Shirt in a relevant enough manner, the manufacturer shall consider changing the supplier for their accessory.

5.2.2 Applicable Directives and Standards

The directives and hENs applicable to the Product were defined based on the scope of the becoming manufacturer, i.e. medical devices, and on specific product features concerning the Device, including the embedded software, and the Analysis Software. In addition, while defining the relative hENs for the design and development of the Device, it was assumed that its intended purpose does not include any mentioning of the ECG or acceleration.

Directive 1999/5/EC on radio and telecommunications terminal equipment, as well as the standard EN 60950- 1:2005 on information technology equipment were included to the list of regulations potentially applicable to the Product, because wireless data transmission between different product components has been considered. Currently, wireless transmission is defined as the desired way for changing the data between different components of the measurement equipment, because of which the related devices need to be designed and validated according to the mentioned requirements.

The manufacturer is expected to challenge the compilation of the required regulatory documents and strive to find any other requirements and/or standards possibly applicable to the Product. For example, if the ECG is found as a relevant feature of the Device after all, or is included to the product in the future, at least two additional standards addressing the development of an ECG measuring device needs to be considered. The standards relevant for the development of an ECG measuring system within the IP application include the EN 60601-2-47 concerning particular requirements for the basic safety and essential performance of ambulatory i.e. portable ECG systems and the EN ISO 11073-10406 concerning personal health device communication and particularly devices for 1-3 lead ECG measurement.

Additionally, the manufacturer has considered the possibility of including an alarm to the Device to alert the user to problems occurring in the electrode-skin interface and/or in the positioning of the Electrodes, for instance. However, the design of an alarm system incorporated into a medical device is regulated and must conform to certain requirements that address to such alarm characteristics as colours of indicator lights used in visual alarms, their flashing frequency, were applicable, and volume used in auditory alarms.

Accordingly, if an alarm is included to the Device design, the manufacturer has to study the related requirements and standardization and at least the standard EN 60601-1-8:2007 and related amendment AC:2010 concerning general requirements for basic safety and essential performance of medical devices. The EN 60601-1-8 discusses the requirements for the design and development, and testing of alarm systems incorporated into medical electrical equipment and medical electrical sys-

tems.

5.2.3 Feasibility Study

The Feasibility Study document produced over the Study was developed gradually through trial and error, as the understanding on medical device regulations, their effect on the manufacturer's processes and on the restrictions they cause increased. The document should be considered initial and directive, representing the current view of the becoming manufacturer.

The feasibility discussions concerning the Product were found extremely fertile especially, as these design and development aspects had not been studied before. Accordingly, the topic that raised most discussion and questions was the overall product concept and especially the different possibilities for the transmission of the measurement data (see Appendix B for example) and the architecture of the Analysis Software.

For instance, wireless technology has reached the consumer markets years ago, but within the hospital environment wireless data transmission and related practices, such as cloud computing, are yet only rarely used. This is because transmitting patient data, related measurements and test results via wireless transmission routes in and out of an abstract server involves issues such as patient security and confidentiality, e.g. secure data transmission, and those concerning the reliability of the wireless system in general.

However, the concept of wireless data handling is rearing its head also within healthcare, especially within applications intended to be used by individuals for the monitoring of their own well-being (n.d. devices in question are not necessarily qualified as medical devices), so it can be assumed that more and more standardized solutions for such devices and systems are being developed.

5.2.4 Market Requirement Document

The Feasibility Study included discussion on the technological considerations of the Product based on which the MRD was created. Currently the MRD contains the defined requirements for all individual components of the Product (e.g. the Device, the Analysis Software, the Diary, etc.). However, in the future an MRD should be created for all individual components separately. Accordingly, the current MRD is to be considered as a directive document to be used in future activities.

An important observation concerning the electronics of the Device was made in the very beginning of the process. The manufacturer has to define a service life for their Device and other components of the Product within which they ensure that the components operate as intended and that they are able to provide sufficiant

maintenance in cases where the performance of the Device, for example, has been impaired. Accordingly, the manufacturer has to ensure that all components essential to the performance of the Device are available over the whole operating time of the Device.

The components critical to the manufacturer's processes include those having particular features required for the Device to function as intended (e.g. components having particularly small tolerances, particular operational amplifiers and microcontroller(s), and the battery). The battery used in current solution is lithium ion battery and defined as critical component by its nature. Accordingly, the manufacturer has to ensure that the lithium ion battery used within the design of the Device is certificated. If there is no such component available, the manufacturer has to decide whether to use the one found most adequote for the solution and conduct the related testing, or whether to use another model completely, i.e. other than lithium ion, that has already been certificated.

All in all, vital aspects for the adequate design of the Product were specified, and essential features of the related regulation was determined. The becoming manufacturer has been made aware of the remaining regulatory tasks and the amount of the required regulatory control in general. Accordingly, the manufacturer still needs to choose the conformity assessment procedure to follow and establish, implement, execute and monitor the related processes, and processes for their appropriate control. Additionally, the manufacturer has to remain up to date with the becoming medical device regulations discussed within the next sections, and to acknowledge the effect of the becoming changes on the related requirements.

5.3 Changing Regulation for Medical Devices

Due to the invariably increasing pace of the development of different technologies, including that incorporated into medical devices, the related regulatory authorities are forced to continuously further develop and improve the related requirements. More and more comprehensive instructions on the design and development of particular technologies are created and published, essentially changing the overall regulatory framework controlling the activities of medical device manufacturers. Accordingly, the results presented in this Study are always to be assessed against the current medical device regulations.

5.3.1 Instructions for Notified Bodies

On 24 September 2013, the European Commission published new guidance on the designation and supervision of NBs in the field of medical devices (EU regulation

No 920/2013) i.e. the MDD and the AIMDD, and on the audits and assessments performed by the NBs (recommendation 2013/473/EC). As all the EU legislation, both documents can be found from the official website of the European Commission free of charge. [35]

The new regulation was created based on the authorities' concerns that the rapid development of medical technologies may have a negative effect on the competence of the NBs and on the validity and adequacy of the assessments performed by them. However, the related modifications do not affect the functions of a medical device manufacturer in any particular manner. [35]

On the other hand, the new recommendation concerning the audits performed by the NB has an evident, though indirect effect on medical device manufacturers, as it addresses the evaluation of their products and their QMS, and the structure of the audit visits paid by the NB. The aspects of the new instructions for the evaluation of the device most relevant to the manufacturer include the following. [35]

Firstly, the NB is encouraged to inspect the product against the directive on Essential Safety and Health Requirements (2006/42/EC). The directive primarily covers machinery, but can be applied to medical system that fulfil the related definition. Secondly, they are instructed to assess the technical documentation of the device provided by the manufacturer against the Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Principles of Medical Devices published by the GHTF. [35] Accordingly, the implementation of the new recommendation emphasis the importance of the use of relevant guidance documents in addition to the related legislation to ensure the adequacy of the manufacturer's processes and the conformity of their product(s) with the related regulation.

Within the assessment of the QMS of a medical device manufacturer the NB is especially recommended to evaluate the adequacy of the system in general and any related processes against the relevant MEDDEVs provided by the European Commission and other documentation when applicable thus, carrying on with the principles described previously. In addition, the NB is advised to require additional testing for products that are suspected not to fulfil their requirements and pay special attention to the risk management activities established by the manufacturer. [35]

The most radical reformation within the NB instruction concerns their audit policy. First of all, the NB is encouraged to audit not only the manufacturer and their premises and/or processes, but those of their critical subcontractors and/or suppliers (e.g. subcontractor providing device components critical to the safety and performance of the device, such as the PCB). Secondly, the NB is instructed to perform one *unannounced* audit every three years. Within these audits, the NB

is to pay special attention to the production of the devices and on any critical processes (e.g. subcontracting, if forming as essential part of the manufacturer's activities). Furthermore, when found necessary or otherwise reasonable, the NB can also subject the unannounced audit to the subcontractor or supplier of the manufacturer according to the same criteria, to especially inspect their product development practices, manufacturing process and testing. [35]

Based on the abovementioned changes, the manufacturer is advised to acknowledge and prepare themselves for these new challenges beginning from 2014 by reviewing their processes for controlling their critical subcontractors and suppliers, and by establishing a system to inform the NB of any relevant changes within their certificated product portfolio, QMS and the design of high-risk devices, if applicable. The manufacturer should also develop a formal operating instruction on how to conduct and control the unannounced NB audits. Additionally, the manufacturer should ensure their awareness of any relevant documents published by the European Commission and that these documents have been integrated into their QMS and the technical documentation of their product(s). [35]

5.3.2 EU Regulation

New EU regulation(s) for medical devices and *In Vitro* diagnostic devices is currently being developed. The regulation is implemented in 2015 at the earliest, but will most probably take longer to be officially recognized. The regulation will replace the current medical device directives i.e. the MDD and the AIMDD and the directive for *In Vitro* diagnostic devices, and accordingly, the related national legislation (e.g. Medical Devices Act 629/2010). [35]

The motivation for developing new regulation originates from the need to increase the safety of medical devices and the harmonization of the related requirements. Additionally, the authorities find it increasingly important to be able to control and monitor the medical device manufacturers and to prevent those whose product(s) does not fully conform to the regulations from entering the EU market. [35]

The content of the becoming regulations is currently being processed by the European Committee and related Committee for health and welfare. The drafts presented by the Committees include numerous new requirements and specifications including those for the definition of cosmetic implants and devices incorporating dead human tissue, increased NB supervision and the requirements for unannounced audits (cp. 920/2013 and 2013/473/EC). The drafts also include new requirements for sufficient clinical evidence, traceability of medical devices i.e. for the implementation of a Unique Device Identifier (UDI; already in use in the US) system and for an extended European database on medical devices, as currently there is only little information available on the European medical device market approvals and related

businesses. [35]

After the implementation of the new medical device regulation, the device manufacturers need to reassess their processes against the new regulation and establish any missing procedures and activities to retain their legal right to sell medical devices within the EU produced under their QMS. However, new guidance on the development of an appropriate QMS is also under development.

5.3.3 Changing Regulation for Quality Management

A survey was conducted in 2011 on the need for change in the current requirements for the quality management of medical devices and the medical device quality standard ISO 13485:2003, respectively. Based on the results, it was discovered that more unambiguous requirements were needed to enable objective and harmonized assessment of the related processes and to ensure that the new requirements enable flexible implementation of new products and quality management techniques. It was also found important that the new requirements cover the whole lifecycle of the product, are suitable for both large and small companies and are also possible for the subcontractor or supplier of a medical device manufacturer to fulfil. [35]

As the abovementioned EU regulation, the main purpose of the changes made to the ISO 13485 is to increase the understanding of the QMSs and the harmonization between different regulatory requirements. Accordingly, the new standard is intended to be compatible with the related requirements by the EU (i.e. EU directives/regulations), the US (FDA) and Japan. The structure of the current standard will remain unchanged. [35]

Actual changes suggested to be made to the ISO 13485 include more specific requirements directed to each individual stage of the overall lifecycle of the product, and for the specification of the organizational roles and related responsibilities. Additionally, the standard shall establish some new terminology and new more specific requirements for the content of the technical file of a medical device. The standard also establishes more specific requirements for the design and development of medical devices, including design and development planning, verification and validation activities, and change management; for the assessment and choice of appropriate suppliers; for the verification of purchased products/components, including the evaluation of related risks; for the processing of customer complaints, and for the control of nonconforming products identified before and after delivery. [35]

Accordingly, medical device regulation are continuously under development and more and more comprehensive requirements are being drawn up. The EU regulations start to resemble those of the US, and it can even be argued that the EU systematically strives to harmonize its regulation with that of the FDA known to

be more intensive and to provide more detailed information of the medical device market approvals. Currently, the market approval received from the US FDA has a lot higher status globally than the CE marking, thus increasing the credibility of the medical device manufacturer and their products worldwide. [21]

6. CONCLUSIONS

Within this Study a product definition for an IP measuring system was created. The definition includes the intended purpose of the product components and their qualification and classification according to the MDD, EU directives and hENs applicable to the product design and development, the study of the feasibility of the product and the definition of the related product specific requirements. The results of the Study shall be utilized by the device manufacturer over the formal design phase of their regulated product development process.

The product definition for the IP measuring system presented in this Study was created for a single product based on the MDD, and does not conform to requirements other than those of the EU and defined for the particular product. The product definition is also to be considered tentative and not legally applicable to the design and development of medical devices within the EU, as such. Additionally, the medical device regulations are currently under a change and the applicability of the results of the Study should thus, be reassessed against the new requirements if implemented over the development phase of the IP measuring system.

Due to the current status of the product and the related processes of the becoming manufacturer, it was clear from the beginning that no final, legally admissable documentation could be produced within this individual Study. However, a comprehensive initial product definition for regulatory purposes was created and guidelines for required future activities were determined. Accordingly, the objectives of the Study can be said to be reached and the Study can thus, be regarded as successful.

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A. APPENDIX

The flow chart in Fig. A.1 illustrates the workflow of the Product as intended by the becoming manufacturer. The workflow is intended to be used as directive and does not discuss any design details.

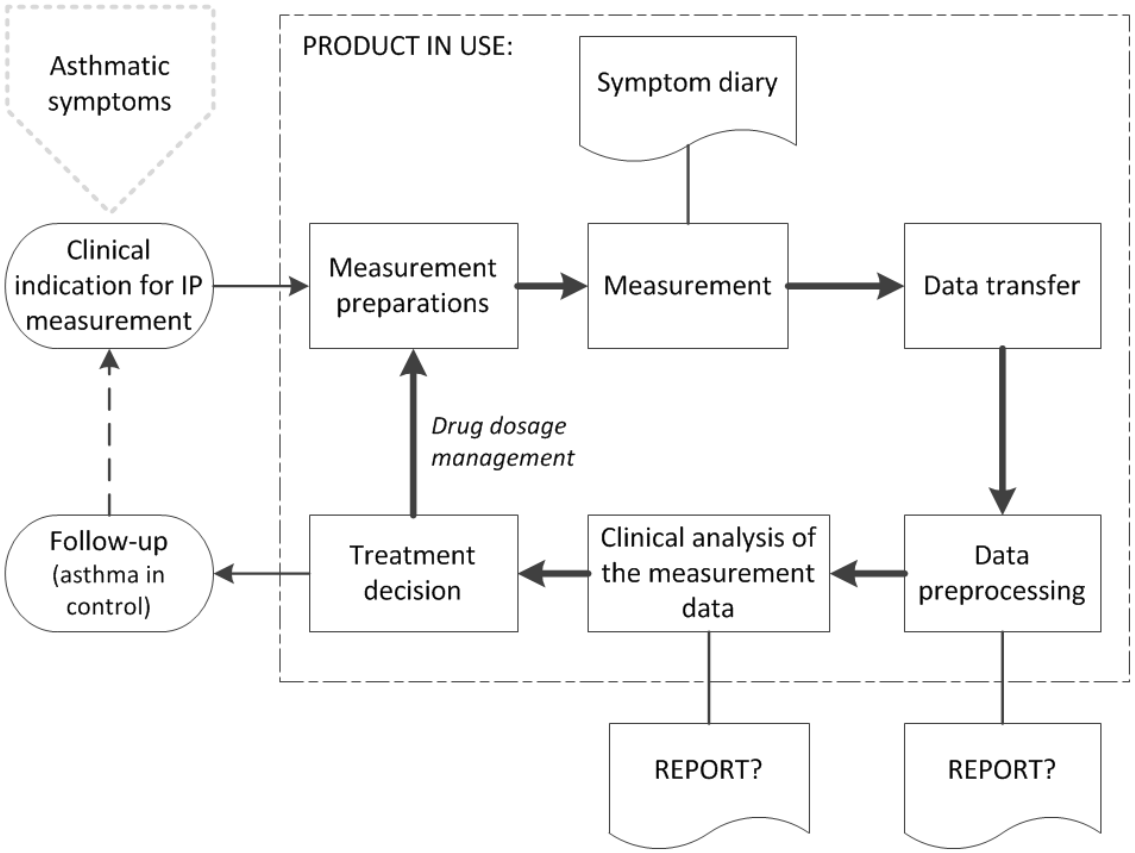

Figure A.1: Intended workflow of the Product while it is in professional use.

Accordingly, the workflow in words is, as follows.

Assumed precondition: Patient is exhibiting asthmatic symptoms.

1. CLINICAL INDICATION: Physician recognizes the need for the use of the Product.
2. MEASUREMENT PREPARATIONS:

Assumed precondition 1: The Device memory is empty.
Assumed precondition 2: The Device battery is full.
Assumed precondition 3: The Device is initialized i.e. paired with a particular patient.

The measurement is prepared in a healthcare facility and/or in home healthcare environment. Preparations include the following:

2.1. State of the Device memory is checked and it is emptied, when applicable.
2.2. State of the Device battery is checked and it is charged, when applicable.
2.3. The Electrodes are attached to the patient according to instructions.
2.4. The Shirt is put on the patient.
2.5. The electrode cables are arranged as instructed and connected to the Device.
2.6. The Device is put inside the Shirt pocket.

3. MEASUREMENT: The measurement is conducted either in a healthcare facility or in home healthcare environment. One measurement event includes the following steps:

3.1. The Device in turned on (the measurement begins and is continued overnight).
3.2. Guardian(s) of the patient or other appropriate party fills in the Diary according to instructions.
3.3. The Device is turned off (the measurement ends).
3.4. The electrode cables are disconnected from the Device and the Electrodes.
3.5. The Electrodes are detached from the patient (the skin is cleaned if needed).
3.6. Used Electrodes are disposed according to instructions.

4. DATA TRANSFER: Measurement data is transferred from the Device in defined manner and stored in an appropriate location according to instructions.
5. PREPROCESSING: Transferred data is pre-processed by a person having the qualification to do so. Pre-processing may result in a report (in electrical form).
6. CLINICAL ANALYSIS: Physician makes a diagnosis based on the processed measurement data (and the report). Clinical analysis may result in another report (in electrical form).
7. TREATMENT DECISION: Decision on treatment is made based on the diagnosis. If no further treatment is required, the process ends. If further treatment is required, the process returns to item 2 for treatment management and/or follow-up.

B. APPENDIX

The workflow described in Appendix A can be achieved by various different product solutions. Accordingly, the following Figs B.1, B.2, B.3, B.4 and B.5 describe some of the potential Product concepts designed based on the feasibility considerations of the becoming manufacturer. The solutions mainly differ in the manner of data transmission from the Device memory to the Analysis Software. Different product components discussed in the Figs describe different components or related articles the becoming manufacturer has to develop for the solution to be complete.

Fig. B.1 discusses quite a basic Product design where the Device has a separate charger and is connected to a computer via a wired connection or via a docking station. The docking station is used for both data transmission and the Device charging (galvanic connection). The Analysis Software is installed on a local server and data transmission from the docking station to a computer is performed either by using a wired or a wireless connection.

Fig. B.2 describes a similar situation as shown in Fig. B.1 which includes the docking station. However, within this solution the Device is charged and the data transmitted from the Device to the docking station via an inductive link (no galvanic connection between the Device and the docking station).

Figs B.3 and B.4 describe the same situation. Accordingly, the Device transmits the measurement data to a smart phone or a tablet computer via wired (see Fig. B.3) or wireless connection (see Fig. B.4). The data is then forwarded by the used equipment to a computer using an internet connection. The Analysis Software is installed on a cloud server and thus, used via an internet connection. To realize this solution, the becoming manufacturer has to establish an additional mobile application to enable the handling of the measurement data using a smart phone or a tablet computer.

Fig. B.5 describes an ideal, but an unlikely solution where the Device itself or the docking station, respectively, incorporates an internet link for the transmission of the measurement data using an internet connection. Furthermore, the Analysis Software is installed on a cloud server. However, transmitting the measurement data in described manner requires a lot of energy thus, making it unlikely that the Device itself could incorporate the required technology.

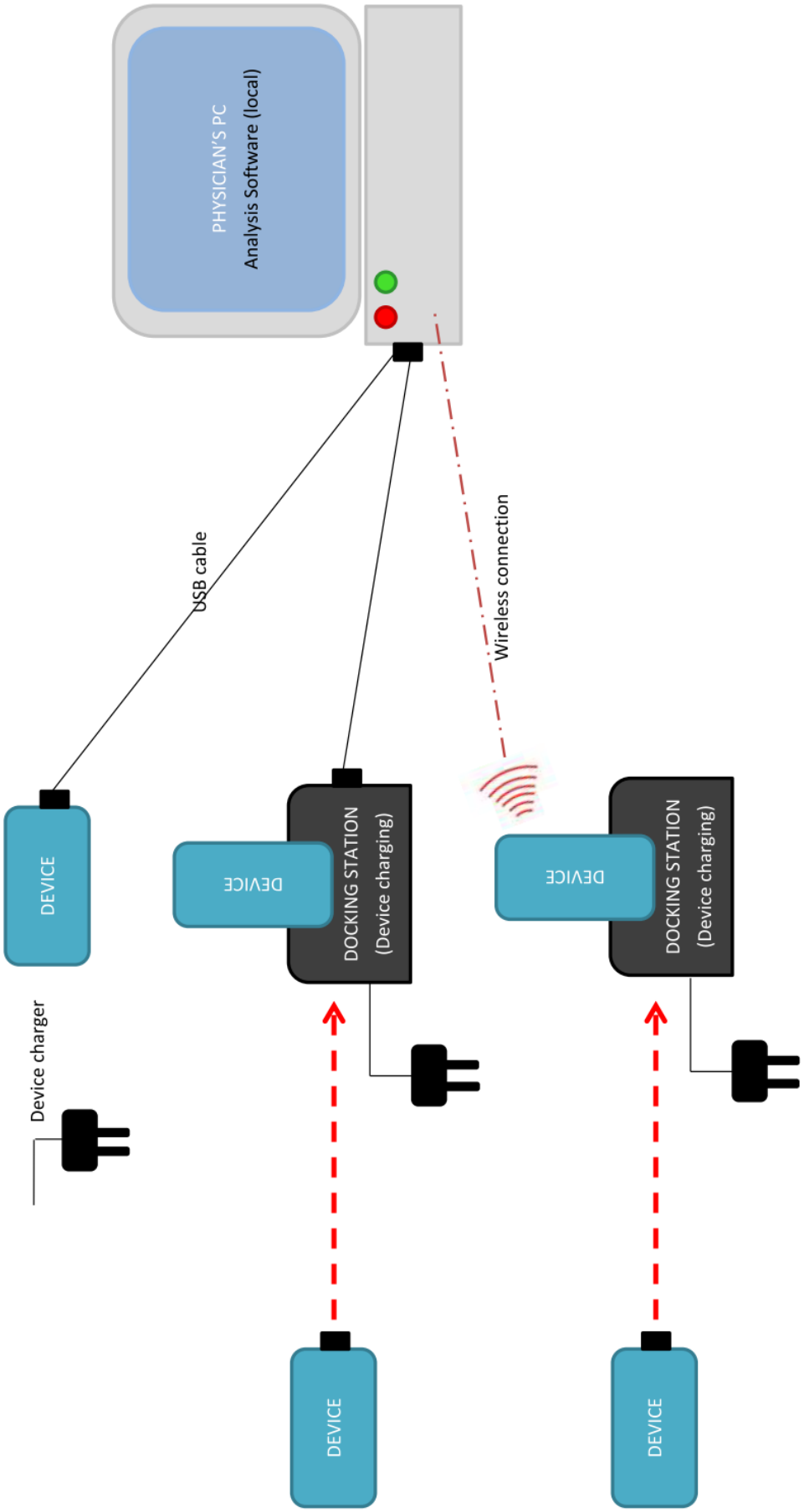

Figure B.1: The Device is connected to a computer via a wired connection or using a docking station. The Analysis Software is installed on a local server.

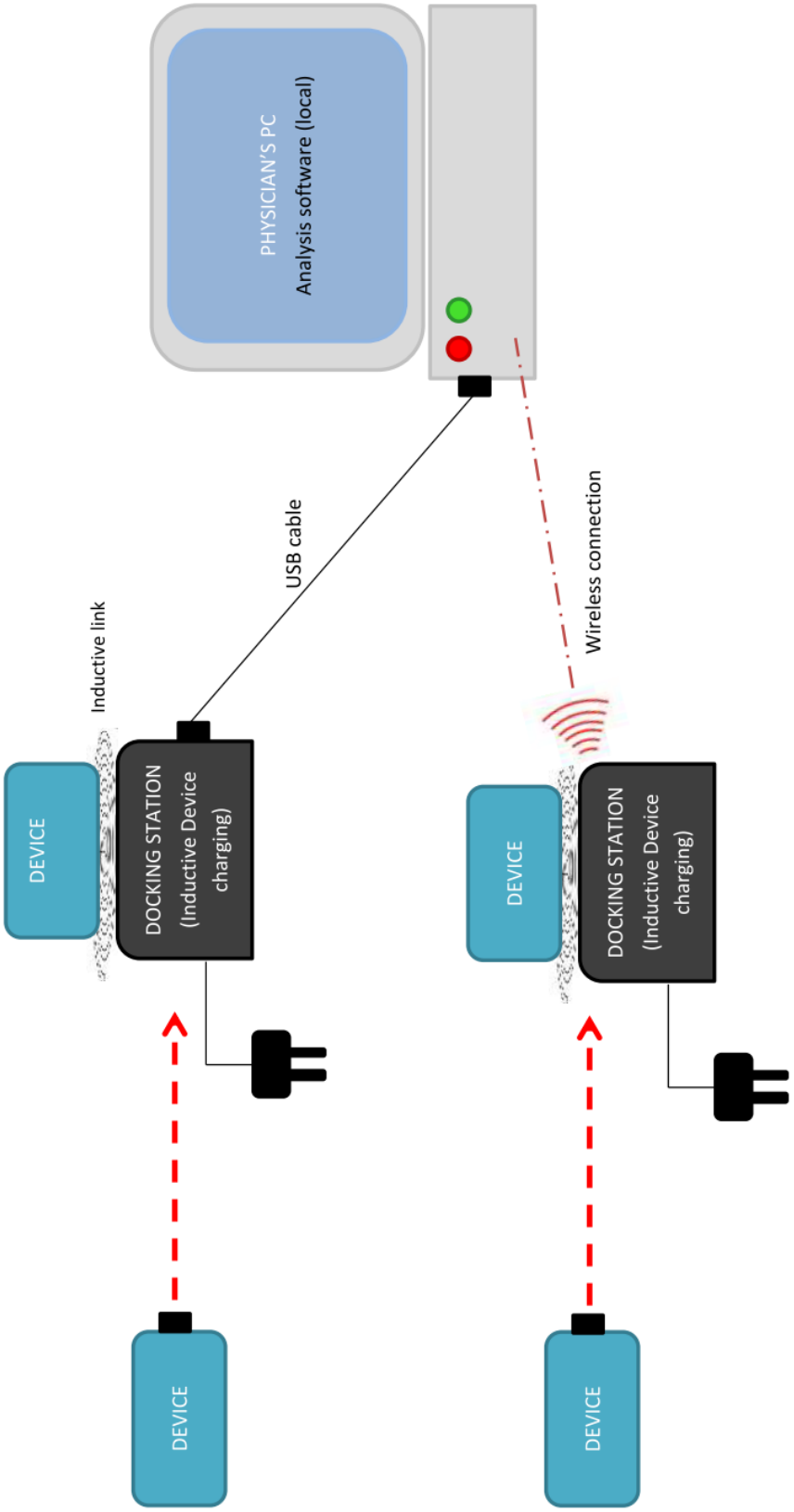

Figure B.2: The Device is connected to a docking station via an inductive link. The Analysis Software is installed on a local server.

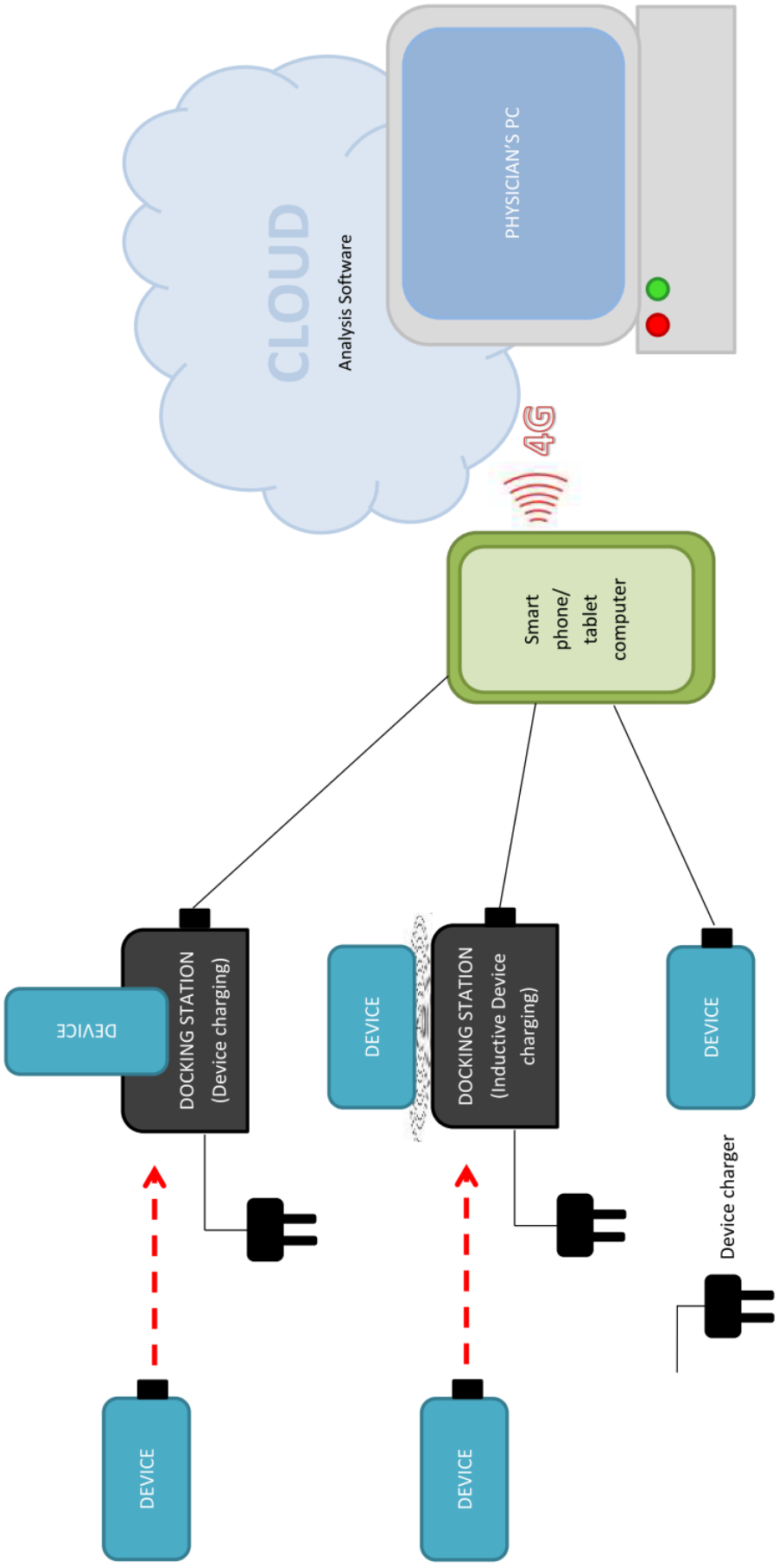

Figure B.3: The measurement data is transmitted from the Device memory to a smart phone or a tablet computer (wired connection) and further to a computer. The Analysis Software is installed on a cloud server.

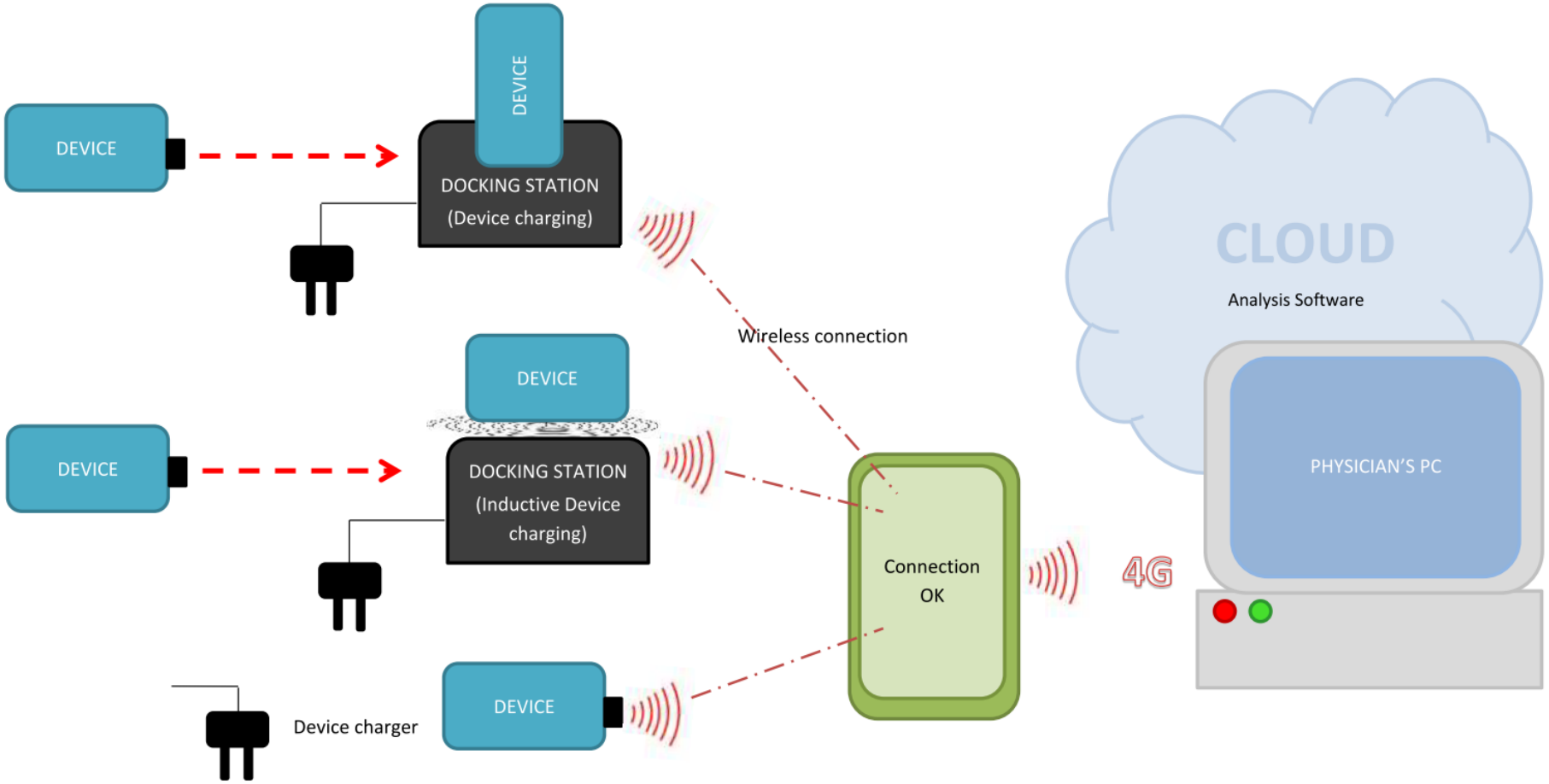

Figure B.4: The measurement data is transmitted from the Device memory to a smart phone or a tablet computer (wireless connection) and further to a computer. The Analysis Software is installed on a cloud server.

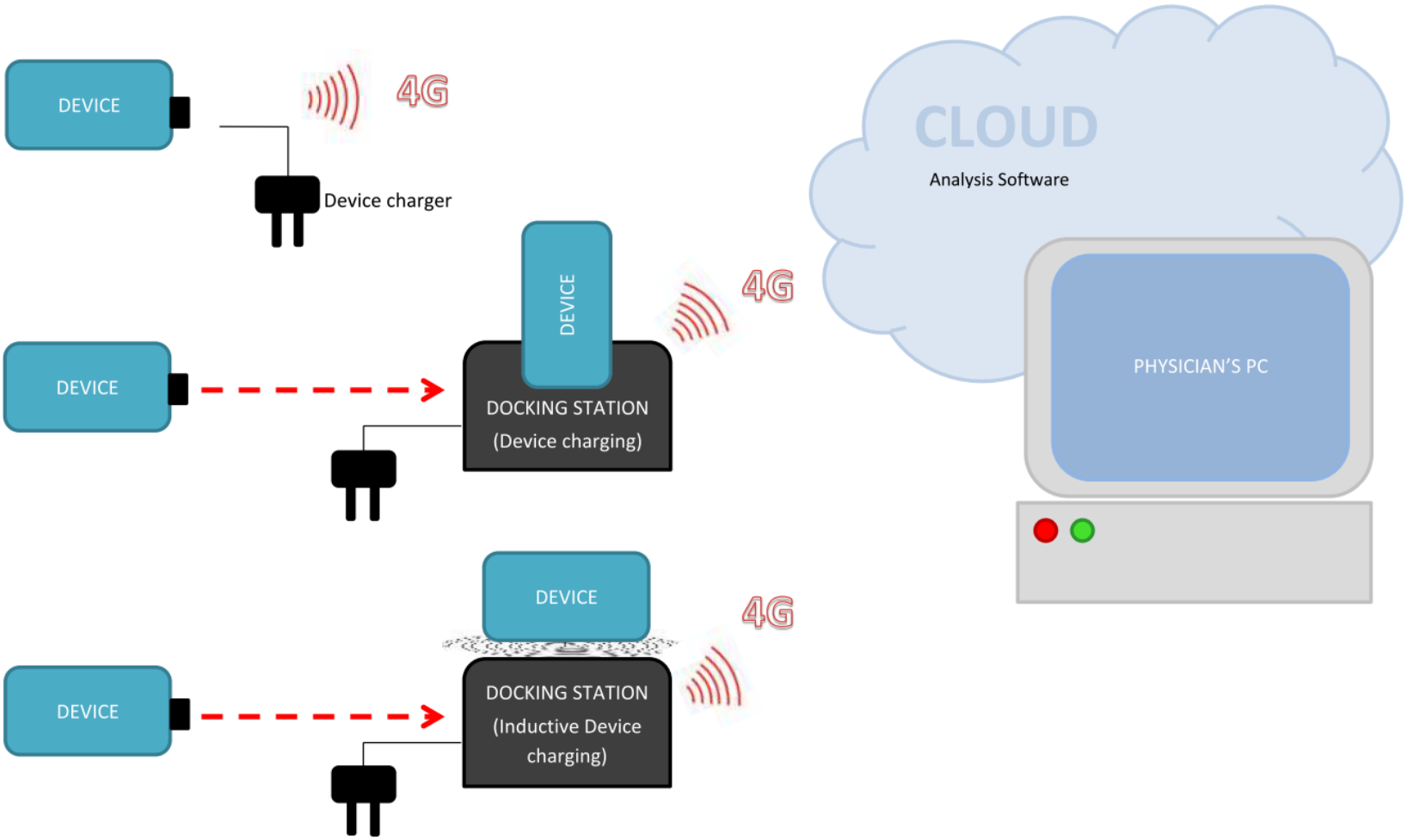

Figure B.5: The measurement data is transmitted to a computer using an internet connection. The Analysis Software is installed on a cloud server.