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DEVELOPMENT AND IMPLEMENTATION OF A QUALITY SYSTEM FOR *IN VITRO* DIAGNOSTIC MEDICAL SOFTWARE

Master´s Programme in Chemical, Biochemical and Materials Engineering
Major in Biotechnology

Master's thesis for the degree of Master of Science in Technology submitted for inspection, Espoo, 17th of December, 2021.

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Abstract of master's thesis

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Abstract

New regulations set by European parliament and the Council of the European Union on medical devices and *in vitro* diagnostic medical devices obligate the economic operators to implement a quality management system. The objective of this Master's thesis is to develop and implement a quality management system for the omnomicsNGS genetic tool produced by Euformatics. During the process of sequencing, raw data from a genome is obtained. This data is analysed and compared to a reference genome. Variant call format file indicates the mutations present in the genome. The omnomicsNGS software highlights the most important mutations in the genome and this information can be used in diagnostics.

Semi-structured interviews with six Finnish medical device companies were conducted to provide guidance in combination with literature research for implementing a quality management system that would fulfil the minimum regulatory requirements and be compatible with agile software development. The implementation was done for ISO 13485:2016 requirements, focusing on the quality management system structure, standards operating procedures and software development processes. Risk management system was implemented according to ISO 14971:2019 requirements.

The results suggest that agile software development process can be adapted to be compliant with ISO 13485:2016 documentation requirements. Documentation requirements increased specially for risk management, product release, improvements and monitoring of the product. The lack of guidance on *in vitro* diagnostic regulation compliance and the lack of resources for CE certification in Europe remain challenges for economic operators.

Keywords Quality management system, medical device, *in vitro* diagnostic, medical software, software development, risk management

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Tiivistelmä

Euroopan parlamentti ja Euroopan unionin neuvoston uudet asetukset lääkinnällisille laitteille ja *in vitro*-diagnostiikkaan tarkoitetuille laitteille velvoittavat talouden toimijoita rakentamaan laadunhallintajärjestelmän. Tämän diplomityön tavoite on kehittää ja toteuttaa laadunhallintajärjestelmä Euformaticsin valmistamalle omnomicsNGS-työkalulle. Sekvensointiprosessissa saadaan raakadataa genomista. Tätä dataa voidaan analysoida ja verrata referenssigenomiin. Variant call format -tiedosto osoittaa genomin tärkeimmät mutaatiot ja tätä informaatiota voidaan käyttää diagnosoinnissa.

Laadunhallintajärjestelmän toteutuksessa hyödynnettiin teemahaastatteluita kuuden suomalaisten lääkinnällisiä laitteita valmistavan yritysten kanssa ja kirjallisuustutkimusta niin, että järjestelmä täyttäisi regulatiiviset vähimmäisvaatimukset. Laatujärjestelmä toteutettiin ISO 13485:2016 vaatimusten mukaisesti, keskittyen laadunhallintajärjestelmän rakenteeseen, vakiotoimintamenettelyihin ja ohjelmistokehitysprosessiin. Riskinhallintajärjestelmä toteutettiin ISO 14971:2019 mukaisesti.

Tulosten perusteella voidaan päätellä, että ketterää ohjelmistokehitystä voidaan muokata ISO 13485:2016 dokumentaatiovaatimusten mukaiseksi. Dokumentaatiovaatimukset lisääntyivät erityisesti riskinhallintaprosessille, ohjelmiston julkaisemisprosessille ja tuotteen parantamiselle sekä valvonnalle. Ohjedokumenttien vähyys *in vitro*-diagnostiikkaan tarkoitettujen laitteiden asetuksen noudattamisesta ja resurssien vähyys CE-sertifiointiin Euroopassa aiheuttavat haasteita talouden toimijoille.

Avainsanat Laadunhallintajärjestelmä, lääkinnällinen laite, *in vitro*-diagnostiikka, lääkinnällinen ohjelmisto, ohjelmistokehitys, riskinhallinta

Preface

Writing this thesis has been an interesting and rewarding experience. I would like to thank my supervisor professor Marko Nieminen and my advisor Tommi Kaasalainen for providing guidance and feedback during the process. Thank you to my colleagues at Euformatics for their contribution, questions, feedback and ideas for the quality management system and thank you to Dr. Christophe Roos for providing feedback for the thesis. Thank you to the professionals who participated to my interview and gave me their time, expertise and advice.

Espoo, 17.12.2021

Iina Kivimäki

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Abbreviations

AIDC	Automated Identification for Data Capture
AIMD	Active Implantable Medical Devices
AIMDD	Active Implantable Medical Devices Directive
AMDD	Asian medical device directive
AMP	Association of Molecular Pathology
ASCO	American Society of Clinical Oncology
ASEAN	Association of Southeast Asian Nations
BAM	Binary alignment map file format for sequencing data
BCR	Balanced chromosomal rearrangement
CAP	College of American Pathologists
CAPA	Corrective and Preventative Actions
CE	Conformité Européenne, CE mark
CEN	European Committee for Standardisation
CGMP	Current Good Manufacturing Practices
CNV	Copy number variant
EUDAMED	European database on medical devices
FASTQ	Raw sequencing data file format
FDA	United States Food and Drugs Administration
GHTF	Global Harmonizing Task Force
GLP	Good Laboratory Practices
GRC	Genome Reference Consortium
GRCh37	Genome Reference Consortium Human Build 37
GRCh38	Genome Reference Consortium Human Build 38
HRI	Human readable interpretation
IEC	International Electrotechnical Commission
Indel	Small insertions and deletions in a genome
ISO	International Organization for Standardization

IVD	*In vitro* diagnostics
IMDRF	International Medical Device Regulators Forum
IVDMD	*In vitro* diagnostic medical device
IVDD	*In vitro* Diagnostic Directive 98/79/EC
IVDR	*In vitro* Diagnostic Regulation 2017/746
LDT	Laboratory-developed test
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive 93/42/EEC
MDR	Medical Device Regulation 2017/745
NGS	Next Generation Sequencing
PIP	Poly Implant Prothèse
QMS	Quality management system
SNV	Single nucleotide variants
SOP	Standard Operation Processes
SV	Structural variant
UDI	Unique Device Identification
UDI-DI	UDI device identifier
UDI-PI	UDI production identifier
VCF	Variant call format
WGS	Whole Genome Sequencing
WHO	World Health Organization

1 Introduction

According to the World Health Organization (WHO), medical devices are defined as any tool, instrument, reagent, software or material that is intended for diagnosis, monitoring, or providing information by examination of human specimens (World Health Organization, 2021). Currently, the European Parliament and the Council of the European Union (2017a; 2017b) have divided the regulation of medical devices into Medical Device Regulation 2017/745 (MDR) and *In vitro* Diagnostic Regulation 2017/746 (IVDR). EU 2017/746 concerns *in vitro* diagnostic medical devices and accessories. *In vitro* diagnostic medical devices (IVDMD) are a subclass of medical devices that are used in studying human specimens. These devices are defined in Article 2 of the regulation: "*in vitro* diagnostic medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological process or state
(b) concerning congenital physical or mental impairments
(c) concerning the predisposition to a medical condition or a disease
(d) to determine the safety and compatibility with potential recipients
(e) to predict treatment response or reactions
(f) to define or monitoring therapeutic measures." (European Parliament & Council of the European Union, 2017b)

The Global Harmonizing Task Force (GHTF) was created in 1993 to ensure safety and implementing common guidelines for the medical device industry and governing

them from pre-market to post-market quality. The guidelines were developed by study groups consisting of national medical device authorities and medical device industry representatives. GHTF guidelines are the basis of local regulations around the world. (Cheng, 2003)

Based on GHTF recommendations the International Organization for Standardization developed ISO 15225:2000 *Nomenclature – Specification for a nomenclature system for medical devices for the purposes of regulatory data exchange standard*. The development of this standard has led to more detailed and updated standards that guide medical device regulation currently (Cheng, 2003). Consequently, *The European Council directive 93/42/EEC of 14 June 1993 concerning medical devices* (MDD) and *Directive 98/79/EC of The European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices* (IVDD) were implemented in Europe to regulate medical devices and IVDMDs (Council of The European Communities, 1993; European Parliament & Council of the European Union, 1998).

Patients are relying on medical devices for accuracy and safety in their treatment and healthcare. The usage of medical devices and their critical nature in patient care is increasing. This makes regulation, validation, and quality systems of medical devices important. In Europe, regulations were made and updated to ensure safety and performance of the medical device. When the medical device follows European legislation and is assessed by a notified body or the manufacturer itself to indicate conformity, CE-marking can be attached to the product. CE-marked product can be marketed as a medical device in Europe. (Melvin & Torre, 2019)

According to the European parliament and the Council of the European Union, the IVDR must be applied before 26th of May 2022 by economic operators in Europe. This regulation applies to software tools used in diagnostics of genetic mutations and conditions with a genetic component. This thesis concerns specifically such tools. The IVDR obligates the manufacturers of *in vitro* diagnostic medical devices to validate the device and to provide evidence on the safety and effectiveness on the device. Previously, diagnostic and research laboratories using such devices for genetic testing

have themselves been able to account for the quality management system (QMS) for the entire process of sequencing form acquiring the specimen to diagnosis. Under the IVDR, the manufacturer of an IVD device must implement their own QMS. (European Parliament & Council of the European Union, 2017b)

The objective of the thesis is to describe the development and implementation of a quality system for *in vitro* medical device according to the IVDR regulations. The tool in focus is the omnomicsNGS genomic data interpretation software tool developed and produced by Euformatics Oy in Finland. The quality system must include documentation of all the steps in the development process of the tool and support the usability of the product. The thesis focuses on developing and implementing this quality system based on current quality standards and regulations.

This thesis aims at answering the following research questions:

What are the minimum requirements for implementing a quality system that is not too laborious for a manufacturer to maintain and is simultaneously beneficial in terms of patient safety?

What kind of software development method can be used in the medical device framework?

How does the development process produce a tool that can be trusted by the user?

How can the quality system ensure that the product is able to compete on the market and does not lower the usability of the product?

This thesis analyses the regulatory requirements and puts them into perspective of the genetic tool, its operational environment and the possibilities of development. The quality system must be able to demonstrate that the manufacturer of a medical software operates according to the regulations. The software development process must be receptive to changes and customer requests, while producing records of the product requirements, implementation and testing.

Very little is still known about the human genome and the field of molecular genetics research is extremely dynamic. **How can the quality system be set in place without hindering the tool from swiftly evolving together with the field of molecular genetics?**

This thesis also aims to answer **how other medical device companies are developing their QMS to comply with the IVDR or the MDR.**

Chapter 2 of the thesis discusses product development, starting from general product development, then focusing on medical device development and finally, specifically *in vitro* diagnostic software development. Chapter 3 outlines the standards that are related to medical devices and medical device software. Chapter 4 focuses on the EU regulations for medical devices and then looks at global regulations. Chapter 5 summarises chapters 2 to 4 to outline the motivation for the thesis; the QMS framework for a variant interpretation software. The methods used in the thesis are presented in chapter 6. Chapter 7 introduces the QMS model constructed based on the research and the collected data. Chapter 8 presents the results from the interviews and the developed quality management system model. Chapter 9 discusses the results and connects them to previous research. The future of *in vitro* diagnostic medical devices regulation is also discussed. The research questions defined in the introduction chapter are answered and recommendations for future work are given in chapter 10.

2 Medical device development

In this chapter, the concepts of product development are presented, focusing on medical device development and software development. These ideas are combined in section 2.3, where *in vitro* diagnostic software development is explored.

2.1 General product development and medical device development

Product development is essential for organisations' success and survival. Companies that quickly develop products that catch the consumer's attention are more likely to succeed than other companies. The main steps of a product development are presented in Figure 1. The literature review of Brown & Eisenhardt (1995) highlights three research streams of product development. These streams are Rational plan, Communication web and Disciplined problem solving. The key ideas of the Rational plan are that the company has a superior product with an attractive market and the customers are involved early in the development process. This stream would produce a high-quality and cost-effective product. The success of the Communication web would be based on internal communication between the development team and external communication with outside sources, which would enhance the performance of the company. The third stream, Disciplined problem solving consist of a problem-solving development team and a strong management overlooking the product vision. (Brown & Eisenhardt, 1995)

Figure 1. Product development process (da Luz et al., 2018).

Product development consists of six main phases. The process starts with planning, which aims to develop a product with better characteristics than other products on the market or a product from a new idea. In the conceptual design phase, the

solutions found in the planning phase are analysed and elaborated to find the best solution. Next, a detailed design is made based on the results of the previous phase. Final specifications are made to the design. Testing / prototype phase verifies that the realistic implementation of the product requirements is possible and allows changes to be made to the design based on testing results. The result of this phase is a prototype of the product. In the production / market launch phase the production is started, and the characteristics and benefits of the products are communicated to potential customers to create a potential market for the product. The next phase of product development is product review. This phase is used to review all the previous phases and to develop the product development process. Similar products can be used as a reference in the beginning of the development process to have more data to review. (da Luz et al., 2018)

Medical devices are developed based on similar principal as the general product development but additionally there are regulations and standards that a medical device manufacturer needs to follow to ensure the safety of patients and effectiveness of the product throughout its life cycle. The legal framework of medical device regulation might be difficult to navigate as contradictions can occur even inside one regulatory system. The design of a medical device needs to consider the safety and performance when the device is used as intended by the manufacturer. The device must be clinically effective which needs to be proven with clinical evidence. A manufacturer needs to collect scientific and clinical evidence of the device during testing and product review phases. Benefits associated with the use of the device must outweigh the risks for a patient or a user. A medical device manufacturer must also consider the chemical, physical and biological properties and how the device is compatible with biological tissues if applicable for the device type. For example, microbial contamination must be controlled by the manufacturer and guidance provided for the user. The requirements for the medical device manufacturer are dependent on the risk associated with the use of the device. The risk classification is usually based on the risk to patients and users, degree of invasiveness in the human body and duration of the use. Regulatory authorities

regulate medical device manufacturers and provide guidance on the medical device regulations. (Altayyar, 2020)

Py et al. (2021) describe usability as “the degree to which a product can be used by identified users, to achieve defined goals effectively, efficiency and satisfaction, in a specified context of use”. Usability in medical devices is an important factor, as the safety of the patients must be a priority. EU 2017/746 and 2017/745 both require conformity assessments from manufacturers to proof the usability and safety of their devices. It is crucial to involve users to the medical device development process to assess the user experience and address problems that the device may have. (Py et al., 2021)

More clinical evidence is needed for medical devices under the new regulations (the IVRD and the MDR) than under the medical device and *in vitro* diagnostic directives. Notified bodies, independent regulatory bodies in Europe, will more carefully examine the benefit-risk ratios, the QMS and the quality of clinical data in conformity assessments. End-users can be involved in clinical studies to have valuable information from the real user environment. (European Parliament & Council of the European Union, 2017a; 2017b; Py et al., 2021)

The International Electrotechnical Commission (IEC) 62366:2015 standard describes the usability of medical devices. The development of usability of the device minimis the user errors and risks associated with use. The standard contains requirements for application specification, identification of usability-related dangers, usability specification and requirements for validation and verification of usability. The standard states the regulatory requirements, but it does not define techniques to implement the requirements or the methods to evaluate them. Scherer & Gouveia Filho (2019) suggest a documentation template for the usability engineering process. They suggest that usability is considered in different contexts, adding detailed user profiles for intended users, requirements for the user interface, use scenarios, risk analysis and management. For verification and validation of usability they suggest

user satisfaction questionnaires, audits, blind testing, and expert reviews. (Scherer & Gouveia Filho, 2019)

2.2 Software development

Traditionally, software has been developed according to the waterfall model or the V-model. With the waterfall model, requirements are first defined and then software is designed, focusing on process documentation and traceability. The V-model encourages the planning of testing phases alongside the development phases. Developing according to these traditional software development models is thus slow to respond to quickly changing requirements and user requirements. Agile development processes have been designed to meet more rapidly changing requirements. (Heeager & Nielsen, 2018; Kostić, 2017)

Agile software development methods aim to deliver customer requirements as efficiently as possible. Agile process consists of iterations where code can be quickly developed to meet customer needs instead of aiming to deliver the software in the final form. However, according to ISO 14971 risk management standard and IEC 62304 software life cycle processes, medical software needs to be fully tested and verified before a release. (Kostić, 2017)

Scrum is one of the most popular Agile methodologies. Scrum consists of incremental time periods called sprints during which the development team works on developing product features. The content of a sprint is decided on a sprint planning session, where product requirements are pulled from the product backlog. The progress of development is evaluated during a sprint review session. (Stirbu & Mikkonen, 2018) The Scrum method is presented in Figure 2.

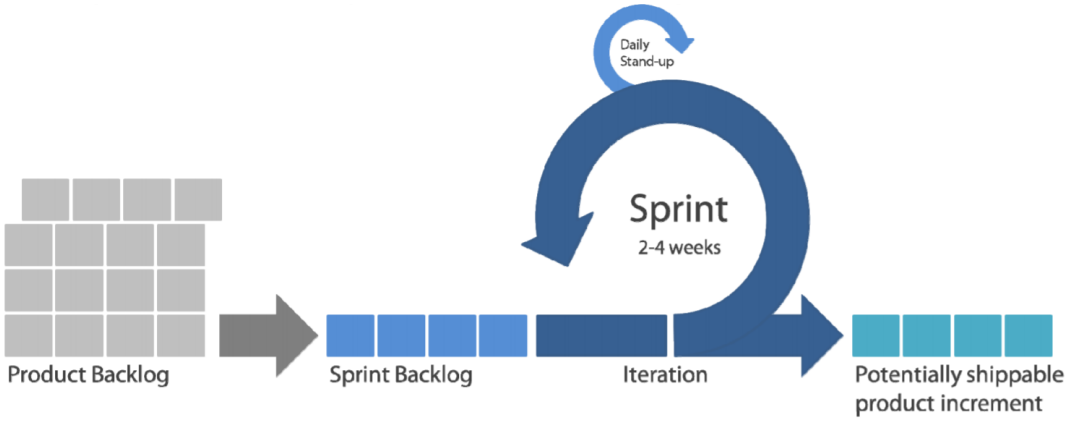

Figure 2. Scrum methodology (Hammad & Inayat 2018).

Agile software development processes are highly iterative and incremental. However, iterative processes are not completely compatible with safety-critical development. It can be questioned if agile methods are suitable in the context of medical device development, where it is important to record all the development steps. Heeager & Nielsen (2018) have conducted a literature review on safety-critical software development based on agile methods, that include medical device software and IVD software. The review found that agile methods do not contradict regulatory requirements and it is possible to use agile methods in safety-critical context, but often agile methods must be modified to meet the regulatory requirements for example by increasing the amount of documentation. The problems found in the review were related to documentation, requirements of user stories, iterative and incremental life cycles, and testing. Maintaining documentation is not essential in agile development, but regulatory requirements oblige proper documentation of all processes as proof of safety and effectiveness. Therefore, following regulatory requirements decreases the use of agile methods in safety-critical software, because the flexibility of the process is decreased. (Heeager & Nielsen, 2018)

Commonly, agile software development aims to have barely sufficient amount of documentation and it is not seen as an essential part of the development process. However, safety-critical software development requires more detailed and high-quality documentation that may have to be audited by regulatory authorities. The review by Heeager & Nielsen points out that it is important to focus on the content

of the documentation to keep it as light as possible while still meeting regulatory requirements. The focus of the documentation should be to verify the safety of the software. The responsibility of documenting could be shifted to a sub-team so that the development team can allocate their time for development work. (Heeager & Nielsen, 2018)

ISO 13485:2016, a standard for medical device quality management system, emphasises that customer requirements should be considered and documented when designing the product as wells as when reviewing the product. Py et al. (2021) state that involving different types of end-users in the manufacturing process provides valuable information of device performance and possible risks associated with use. Users who are involved in the entire life cycle of the device can provide suggestions and solutions for better and safer design of the product. (Py et al., 2021; International Organization for Standardization, 2016)

User stories are descriptions of software features from the customer perspective, located in the product backlog and prioritised by the product owner. For a safety-critical software it is important that all requirements are described in detail and the features need to be verified and validated. More detailed descriptions and ensuring validation and verification testing can prolong the development process. Heeager & Nielsen (2018) suggest separating the safety requirements and functional requirements to different backlogs, as the safety requirements are more stable and change less of the as the frequently changing functional features. A manufacturer could also introduce abuser stories and security related user stories that address the threat scenarios and security concerns related to the use of the software. (Heeager & Nielsen, 2018)

A manufacturer needs to implement a life cycle model that contains a plan for the software life cycle to increase the predictability of the safety-critical software development. Development iterations can be planned with specific goals for a release of the software version which makes the process more predictable. (Heeager & Nielsen, 2018)

The development of agile processes is driven by testing, as all the features developed are tested either manually or with automated testing. Testing is also highly important for safety-critical software development. The V-model focuses on planning for testing in the initial stages of safety-critical software development. Similarly, while using agile methods, manufacturers should focus on the planning of testing. The implementation of verification testing makes the development process more work intensive and less favourable for the usage of agile development methods. (Heeager & Nielsen, 2018, Kostić, 2017) The shortcomings in testing can lead to issues for the users and patients of the safety-critical software. An example of such shortcoming occurred in the hospital district of southern Finland where the usability of the patient record system has been heavily criticised (Paavonen, 2021).

Software development process also needs to include analysis and evaluation of risks. The literature review conducted by Kostić (2017) points out the lack of risk management and quality control with agile methods. Formal specification and testing of software features are needed to decrease risks associated with the use of the software. (Kostić, 2017) If risk management is done as a separate process to the development process, the development process freezes, and new features cannot be added before all risks are assessed. Risk management should be implemented to the design process in small increments as soon as a new risk has been identified. The same system should be used to risk management as the development process. That way the features and risk control measures can be linked for traceability and the control measures can be implemented to the Scrum process. (Stirbu & Mikkonen, 2018)

Formalising the development process increases the safety of the product but can increase the cost of development. Kostić (2017) determines documentation and traceability as the biggest challenge in the implementation of agile processes to medical software development. Documentation is difficult to implement to agile process because requirements of software features can change quickly even in late development phases. (Kostić, 2017) Stirbu & Mikkonen (2018) mention Jira, which is

a project management tool, as a tool that can be used for traceability of between requirements. There are also risk management plug-ins that can be integrated into Jira.

ISO 9000 series on quality management, and specifically ISO 9000-3 on software quality managements, can be used by software manufacturers to ensure the quality of their development process. Quality requirements should be established by the company managements. Software quality assurance can be determined by planning a quality management approach, engineering techniques, technical reviews, testing strategy, documentation control and a strategy to comply with software development standards. The software testing process should be based on planning the testing process and test cases, determining the methodologies and tools and ensuring that the employees value and function according to defined processes. (Gill, 2005)

2.3 IVD software development

This chapter outlines the next generation sequencing technology and the analysis pipeline and then focuses on IVD software development in the context of software with a medical purpose included into the next generation sequencing pipeline.

2.3.1 The concept of reference genome

The Human Genome Project led to the sequencing of human genome in 2001. This effort has led to the understanding of human genome and provided reference data for sequencing and variant interpretation. Accurate reference genome sequences provide the foundation for modern molecular biology and genomics as the interpretation of sequence data to study evolution, gene expression, and epigenetics depends heavily on the quality of the genome assembly used for its alignment. (Lander et al., 2001; Lander, 2011) Genetic data analysis begins with alignment

against a reference genome. Genome Reference Consortium Human Build 37 (GRCh37, also referred as hg19) was released in 2009 by the Genome Reference Consortium (GRC). The GRCh37 has been extensively used in NGS data analysis and is still currently used due to established bioinformatics pipelines. The human reference genome GRCh38 (also referred as hg38) was released in 2013. The GRCh38 has multiple improvements to the previous GRCh37 reference genome. The GRCh38 provides more complete information on the entire genome, including centromere regions, correcting misassembled regions, and filling gaps of the previous reference genome. The GRCh38 provides more reliable data analysis results due to these improvements. Figure 3 describes the construction of a reference genome. (Howe et al., 2021; Guo et al., 2017)

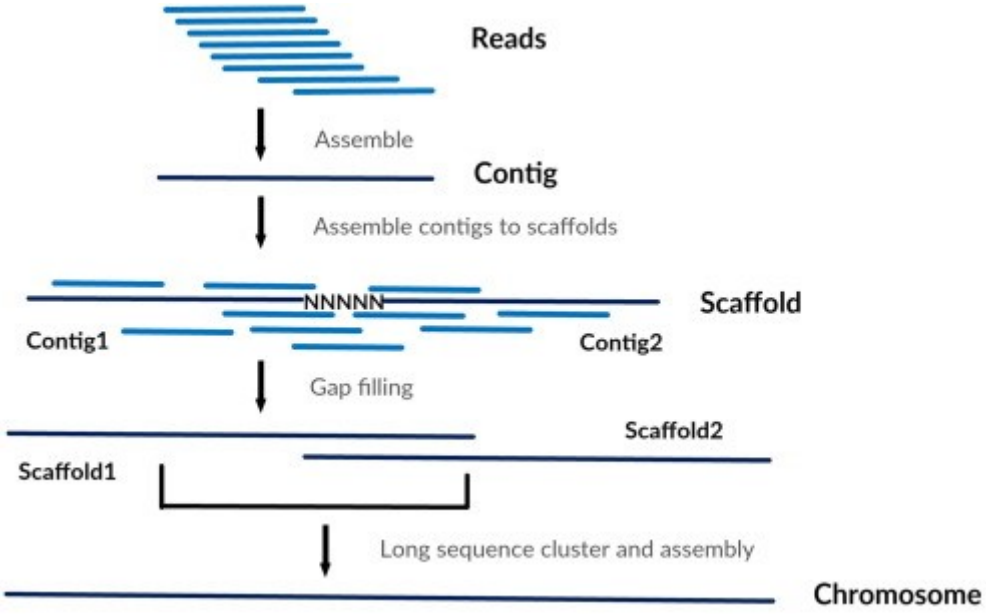

Figure 3. Constructing a reference genome. (Guo et al., 2017)

In the construction of a reference genome, the genome of a species is sequenced in fragments. In theory, the reads cover the whole genome, but heterochromatic regions are usually less well represented. As the reads have overlapping nucleotides, contiguous segments (contig) can be assembled based on the reads. The nucleotide order of a contig is known to a high degree. Scaffolds are formed from multiple contigs. However, there can be gaps between the contigs. The gaps are filled with the

help of genome assembly tools. Finally, the scaffolds are combined to form reference chromosomes. (Cechova, 2021; Guo et al., 2017)

2.3.2 What is a variant?

Sanger sequencing has been the most common sequencing method for single gene sequencing and exon-by-exon analysis (Sanger & Coulson, 1975). Since the beginning to the millennium, the use of high-throughput technologies has increased and speeded up diagnostics of genetic disorders (Ronaghi et al., 1999). These methods produce massive amounts of genetic data in relatively short time and allow fast sequencing of whole genomes. Next generation sequencing (NGS) is a high-throughput technology widely used in genetic testing in clinical laboratories. (Braslavsky et al., 2003; ten Bosch & Grody, 2008)

The goal of genetic testing is often to analyse variants, which are changes in one specific person's genome compared to a reference genome. Variants are commonly categorised in single nucleotide variants (SNVs), small insertions and deletions (indels), and larger structural variants (SVs). Indels are often 1-50 base pair long changes, while SVs are larger than 1000 base pairs. Structural variants are further divided into copy number variants (CNVs) and balanced chromosomal rearrangements (BCRs). CNVs are changes where DNA is lost or multiplied and BCRs are translocations or inversions of DNA. Research and clinical diagnosing of CNVs is important because CNVs account for 1.5% of base genetic variation in genomes while SNVs account for only 0.1%. (Whitford et al., 2019)

2.3.3 Next generation sequencing

NGS generates large amount of data to be analysed. Bioinformatics combines molecules and mathematical and computational methods to study information related to these molecules. The method of data analysis of NGS results is referred as

the NGS bioinformatics pipeline. (Roy et al., 2018) Figure 4 presents the structure of a NGS bioinformatics pipeline.

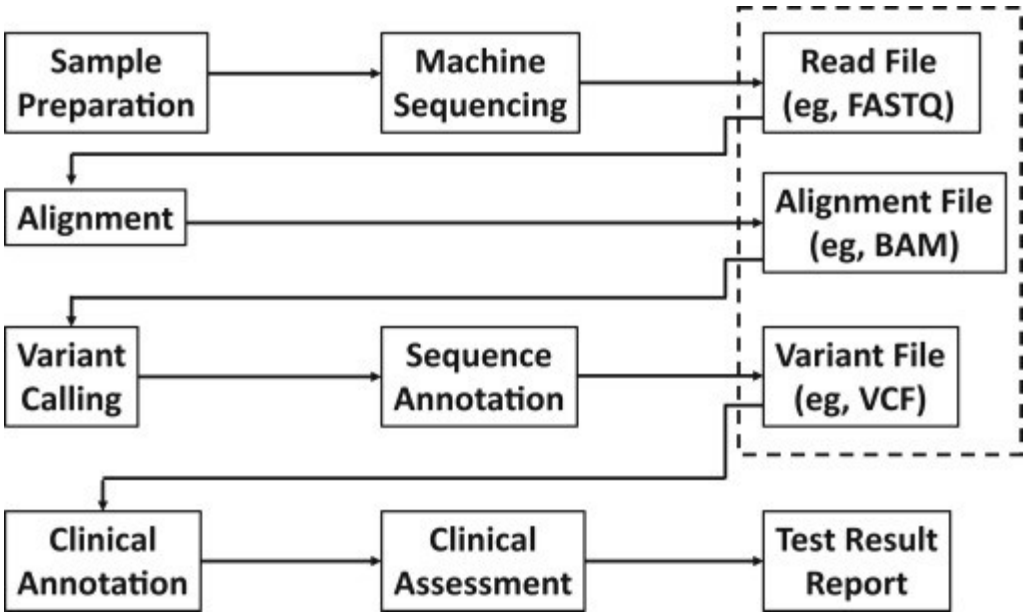

Figure 4. NGS workflow (Lubin et al., 2017).

NGS data analysis consists of primary analysis, secondary analysis, and tertiary analysis. In primary analysis, the genetic sample is sequenced to identify the nucleotides in the sequence. NGS analyses the genome in multiple fragments, most frequently short fragments (75-300 base pairs) as this is the cheapest technology. So called long read sequencing is also offered by the Pacific Bio or the Oxford Nanopore technologies (up to tens of kilobases of sequence per read). The sequenced fragment length defines how long repeated sequences can be bridged. Since there exists a considerable amount of longer repetitive sequences, for example in the heterochromatic regions of the genome, long read sequencing is essential in creating a more comprehensive reference genome build. The short read sequencing is usually sufficient to analyse non-repetitive regions of the genome, which will be the case of most genes and protein-coding regions. Here, fragments of exons are captured and amplified, so that the depth of coverage of targeted sequences is ensured. Depth of coverage is an important concept since the sequencing technology produces errors, both stochastic and dependent on chemical properties of the sequence. In clinical sequencing depth of coverage is an important quality metric. Fluorescent images of

the captured fragments are interpreted with base-calling algorithms and a raw data file of the sequencing run is acquired. A run can contain multiple samples and a so-called demultiplexing step will separate the sequence of the individual samples and store the data in sample-specific files in the *de facto* standard format called FASTQ. The file contains the nucleotide sequence of each fragment and a quality score for every base in the fragment. The type of quality score is dependent on the error model applied by the sequencing platform. (Buermans & den Dunnen, 2014; Di Resta et al., 2021; Roy et al., 2018; Bartha & Győrffy, 2019; Schwarz et al, 2019)

In secondary analysis phase, the fragment sequence data is compared to a reference genome. The short or long reads are aligned with the reference genome and the aligned data is stored in binary alignment map (BAM) file format. A quality score indicates the confidence of the alignment result. BAM file can be further processed before variant calling. Once the sequencing data is aligned, it is possible to identify duplicate reads from the same sequence. These duplicates can then be marked in the BAM file and excluded from further analysis. One option is to do base quality score recalibration, where the base quality scores of sequencing reads are adjusted with an empirical error model. It is also important to conduct quality control of the BAM file before variant calling. Quality control ensures that the sequencing coverage is sufficient for the analysis and that the sample was not contaminated. In the case of family studies, the expected relationships should be confirmed. (Di Resta et al., 2021; Koboldt, 2020; Roy et al., 2018)

Next in the secondary analysis, variant calling is performed. Variant calling is a process where the differences between the sample and the reference genome are identified. Variant calling tools can be applied to individual samples or all samples simultaneously. Variant calling for individual samples may be easier for a clinical laboratory with large number of samples in terms of automating NGS analysis. Secondary analysis results in a variant call format (VCF) file. (Roy et al., 2018; Di Resta et al., 2021; Koboldt, 2020) Figure 5 presents a simple example of a VCF file content.

```
##fileformat=VCFv4.0
##FILTER=<ID=PASS,Description="All filters passed">
##INFO=<ID=GI,Number=1,Type=String,Description="Gene ID">
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
##FORMAT=<ID=AD,Number=.,Type=Integer,Description="Reference,Alternate read depth">
##FORMAT=<ID=DP,Number=1,Type=Integer,Description="Total read depth">
#CHROM  POS        ID           REF  ALT         QUAL  FILTER  INFO       FORMAT     Sample_ID
8       38271151   .            C    T           2410  PASS    GI=FGFR1   GT:AD:DP   1/1:10,240:250
5       79950724   rs1554066076 G    GCCGCAGCGC  3214  PASS    GI=MSH3    GT:AD:DP   0/1:210,240:450
```

Figure 5. An example of a VCF file containing information on two variants.

The first seven rows of this VCF file beginning with # are header lines containing meta-information on how the variant data is presented. CHROM identifies the chromosome the variant is located in. In this example the first variant is located in chromosome 8 and the second variant in chromosome 5. POS indicates the position of the variant in the chromosome. ID gives the unique identifier of the variant. If the ID is unknown, the missing value is expressed as a dot. REF indicates the reference base that is found in the reference genome at the known position. The base or the base sequence found in the sample at the known position are referred as ALT, alternative alleles. In the first variant line the reference base at position 38271151 is C, cytosine and the alternative allele found in the sample in that same position is T, thymine. QUAL presents the quality score associated with the alternative alleles. FILTER shows as PASS if all the filters applied to the variant have passed and a call can be made for the variant. INFO gives additional information on the variant. In this case, INFO gives the gene ID the variant is located in. The first variant is in the fibroblast growth factor receptor 1 (FGFR1) and the second variant is in MutS Homolog 3 (MSH3). FORMAT is an optional field in the VCF that can contain information determined in the header columns. In this file, the format GT:AD:DP refers to genotype (GT), read depth for the reference allele and the alternative allele (AD) and total read depth of the sample (DP). Sample_ID gives the values for the fields in FORMAT. 1/1 that the genotype of the sample is homozygote where both DNA strands have the alternative allele, the reference allele was found 10 times and the alternative allele was found 240 times in the sample. The total read depth was then 250 reads. The genotype of the second sample was a heterozygote, carrying both the reference and the alternative allele. The reference allele was read 210 times and the

alternative allele 240 times, total read depth being 450 reads. (European Bioinformatics Institute, 2021)

2.3.4 Understanding the biological effect of the variants

Tertiary analysis is the bottleneck in clinical genetic analysis. It consists of interpretation of the found variants and identifying their significance including pathogenicity. One fundamental reason for this bottleneck is the relative lack of understanding of the human genome and its ca. 20 000 genes with on average five alternate transcripts for each of them. A specific part of the problem is that many biological functions are dependent on networks of multiple genes, while the variant interpretation quite much still operates on one gene at a time. (Di Resta et al., 2021; Roy et al., 2018)

There are multiple databases containing genomic and variant information based on reference genomes. Common databases include Ensembl for the reference genome and ClinVar, CIViC and OMIM, which contain information on gene annotations, variation frequencies, and disease data. Tertiary analysis consists of variant filtering and classification. Variant annotations are essential for these processes. In tertiary analysis the identified variants are compared with information in multiple variant databases. Aggregated information is then used in the classification and interpretation of the variants. Analysis software can be used to facilitate the process of prioritisation and filtering of variants, making the interpretation process faster and less error-prone for clinical use. The variant annotation process and the algorithms used in filtering variants need to be strictly validated to ensure that clinically significant variants are not missed by the clinician. (Di Resta et al., 2021; Roy et al., 2018)

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) have developed guidance for interpretation of constitutive sequence variants. According to the ACMG best practice guidelines, the

variants are classified into five classes of clinical significance: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. Richards et al. (2015) have defined a list of 28 criteria based on which each variant is evaluated. These criteria include for example variant frequency in reference populations, information from reputable sources, computational predictions, and well-established functional domains. Based on which of the 28 criteria are fulfilled by the variant, a combined statement of clinical significance is determined. Clinicians use these classification criteria in a patient report to guide diagnosis and options for treatment. (Di Resta et al., 2021; Richards et al., 2015; Roy et al., 2018)

For somatic variants the classification is more based on druggability. Here, AMP, American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) proposed a four-category system of classifying and reporting the pathogenicity or clinical impact of somatic variants. Variants in tier I have strong clinical significance and a high level of evidence on diagnosis and therapeutics for specific type of tumours. Variants in tier II have potential clinical significance and multiple published small studies or preclinical trials on the significance. Tier III variants have unknown clinical significance and tier IV variants are benign or likely benign. (Li et al., 2017)

Even though high-throughput technologies make clinical genetic testing more effective, problems remain outside the relatively few genes for which good information is available. However, whole genome sequencing (WGS) is becoming cheaper, and the quality is more even than for captured or amplified libraries. WGS is thus becoming more used for a large number of patients. Problems with WGS still include cost, time, and data storage capacity and in particular processing and interpretation. There also remain technical problems with NGS. Exome wide sequencing is common, but important variants in non-coding regions can be missed with short read sequencing. Human exome contains regions of highly homologous genes as well as pseudogenes where sequence alignment is very difficult and therefore the variants are difficult to analyse. Wrong alignment with the reference

genome can lead to incorrect variant calling, in turn leading to error in diagnosis or treatment and harm to the patient. (Schwarz et al, 2019)

2.3.5 Validation of the technology

NGS technologies have been rapidly developed but rather slowly adopted into clinical use. Due to this late adoption, the guidance on developing and NGS pipelines has only within the last ten years been adjusted to the technical development. The lack of guidance on bioinformatics pipeline validation has led to high variation on validating methods and clinical practises. Insufficient validation and development of pipelines could negatively affect patient's health. The lack of guidance has been addressed by AMP with CAP and the American Medical Informatics Association, who have developed guidelines and best practice consensus standards for the validation of clinical NGS bioinformatics pipelines. The European Molecular Genetics Quality Network (EMQN) and the Genomics Quality Assessment (GenQA) have also been developing methods for NGS pipeline assessment. (Roy et al., 2018; Gutowska-Ding et al., 2020)

Medical devices and IVDMDs must be validated and verified in order to demonstrate conformity with regulatory requirements in the region where the economic operator operates. Validation ensures that the right systems or features are manufactured, and verification ensures that the systems or features are manufacturer in a manner that is safe. (Heeager & Nielsen, 2018) The conformity the requirements is evaluated by notified bodies in European Union (European Parliament & Council of the European Union, 2017a; 2017b). The usability of a medical device should be validated and verified throughout the device life cycle. Evaluation of usability should be used for design inputs, as it brings up possible improvements and new features and reveals bugs in the user interface. Properly done validation and verification functions as proof of safety of the device. (Py et al., 2021)

The computational data analysis structure of NGS is complex. The complexity has led to the use of Sanger sequencing or other less complex sequencing methods as validation evidence of NGS sequencing. AMP recommends that clinical laboratories should validate NGS bioinformatics pipelines themselves. Established pipeline can contain software tools and algorithms for variant calling and annotation that need to be tested for the specific clinical need of the laboratory. Validation should be supervised by professionals with knowledge on NGS interpretation and certification to optimise the safety characteristics of the pipeline. Validation should be performed when the design of the pipeline is optimised. In the familiarisation phase of the pipeline development, errors related to use and design can be eliminated before validation. Validation should be performed in an environment that simulates the user experience in clinical setting and appropriate for the intended clinical use, sample specimen and the variant types intended to study. Each individual components of the bioinformatics pipeline should be validated, reviewed, and approved by qualified professional and laboratory director. The design of the pipeline must follow applicable laws and regulations, laboratory standards and patient information safety must be protected. The test processes and conditions of the pipeline validation must be carefully documented and used samples identified for the traceability of performed studies and results. Quality control and quality assurance parameters must be evaluated during the validation process. Quality control parameters are values computed from control samples or other patient samples and compared to the patient data and quality assurance parameters are data form the individual sample. Integrity of the used data files should be ensured based on quality control measures. When changes are made to the pipeline or the software used in the pipeline, revalidation is needed. (Roy et al., 2018)

Despite AMP recommendations, in Europe the IVDR requires the manufacturer of software in the NGS pipeline, classified as an IVD software, to implements its own QMS. The QMS must include the description and records of the IVD software development process and product realisation. Performance evaluation and post-market surveillance are also required from IVD software as ways to monitor the

safety and effectiveness of the device. The QMS must also include process for vigilance and management of corrective and preventative actions (CAPA). The measures that are defined in the QMS must be proportionate to the risk class of the software. (European Parliament & Council of the European Union, 2017b)

Medical Device Coordination Group guidance MDCG 2019-11 gives additional information on software classification under the IVDR. An IVD software must fulfil the definition of an IVDMD presented in chapter 1 of the thesis and have a medical purpose. The software that driver or influences the use of IVDMD is also an IVD device. An example of this kind of software would be a software driving a sequencer intended for medical purposes. The software used alone or in combination with other devices for analysis, processing or representation of IVD medical information for medical purposes is considered an IVDMD. MDCG 2019-11 gives an example of bioinformatics software intended to analyse raw NGS data to detect and visualise indels and CNVs in patient genomes. This software would be classified as an IVDMD because it is used to provide information on medical condition and processes data coming from and IVDMD. (Medical Device Coordination Group, 2019)

There are no requirements in medical device standards (IEC 62304, ISO 13485) on what kind of development methods or models should be used for medical device or IVD software development. The company can decide based on its own interest if agile or more traditional development methods are used. (Stirbu & Mikkonen, 2018) The manufacturer should consider which development method supports the implementation of IVDR quality requirements.

3 Medical device standards

This chapter presents the most commonly used medical device standards standardisation bodies that define these standards. The contents of ISO 13845 on quality management system and ISO 14971 on risk management are described. Standards for medical device software are presented.

3.1 General medical device standards

International standards provide consistent guidance on documenting medical device manufacturing processes globally and inform the national and international regulations regarding medical devices. These standards are often written by independent nongovernmental bodies that focus on reviewing and updating standards related to development and production of medical devices. Commonly, there is no obligation for a manufacturer to comply with the standards. However, standards can be harmonised with regional regulations and laws and following them is a way to demonstrate conformity of product with the technical requirements e.g. of the EU regulations. In the EU, commonly followed standards for medical device manufacturing are formulated by International Organization for Standardization (ISO), International Medical Device Regulators Forum (IMDRF) and Organization for Economic Co-operation and Development (OECD). Additionally, there are regional guidance documents, including Good Laboratory Practices (GLP). European standards are adopted by European Committee for Standardisation (CEN). (Schuh & Funk, 2019; Your Europe, 2021)

ISO was founded in 1946 to unify industrial standards globally. ISO standards provide guidelines for good practices, health, safety, and environmental requirements. A few of the most important ISO standards for medical device development and quality management systems are ISO 9001:2015 *Quality management systems — Requirements*, ISO 13485:2016 *Medical devices — Quality management systems —*

Requirements for regulatory purposes, and ISO 14971:2019 *Medical devices — Application of risk management to medical devices*. (Lamph, 2012)

Other ISO standards related to medical device manufacturing are ISO 14001 on Environmental Management Systems, ISO 50001:2018 on Energy Management Systems, ISO 45001 on Occupational Health and Safety and ISO 27001 on Information Security Management Systems. ISO 10993 series relates to the biocompatibility of medical devices. The series contains guidance on biological evaluation of medical devices related to for example testing and risk management, toxicity, *in vitro* use, implantation, and degradation. ISO 15223 *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied* guides manufacturers on the content of labels and instruction manuals for medical devices. Similarly, ISO 18113 series informs labelling for IVD devices. IEC 62366-1:2015 *Medical devices – Part 1: Application of usability engineering to medical devices* addresses medical device usability requirements. Additionally, there are standards for sterilisation and aseptic processing of healthcare products, laboratory testing and performance evaluation. (Schuh & Funk, 2019; European Commission, 2020)

The United States Food and Drug Administration (FDA) requires medical device manufacturers to follow current good manufacturing practices (CGMP). CGMPs for a quality management system can be fulfilled by following ISO 13485 which is a QMS standard specific to medical devices modified from ISO 9001. (Lamph, 2012) ISO 13485 contains guidelines for quality management system general requirements, requirements on documentation, management responsibility, resource management, product realisation and measurement, analysis and improvement (ISO 13485). Implementing a quality system will improve the processes of the manufacturers and allows a systematic approach for development of the product. The QMS will enable the manufacturer to systematically collect information on feedback, complaints, the performance of the product and nonconformities. These implementations ensure that the improvements made in manufacturer processes are

well-informed and profitable. (International Organization for Standardization, 2017 practical guide) The topics covered by ISO 13458 are presented in Table 1.

Table 1. The contents of ISO 13485 (International Organization for Standardization, 2016).

Chapter	**Description**
1	Scope
2	Normative references
3	Terms and definitions
4	Quality management system: General requirements, Documentation requirements
5	Management responsibility: Management commitment, Customer focus, Planning, Responsibility, authority and communication, Management review
6	Resource management: Provision of resources, Human resources, Infrastructure, Work environment and contamination control
7	Product realisation: Planning of product realisation, Customer-related processes, Design and development, Purchasing, Production and service provision, Control of monitoring and measurement equipment
8	Measurement, analysis and improvement: General, Monitoring and measurement, Control of non-conforming product, Analysis of data, Improvement
Annex A	Comparison of content between ISO 13485:2003 and ISO 13485:2016
Annex B	Correspondence between ISO 13485:2016 and ISO 9001:2015

The key targets of the ISO 13845 quality management system are meeting requirements of the organisation, customers and regulations, meaning the MDR or the IVDR in Europe and relevant standards, and documenting of these requirements. The personnel of a company must be trained to comply with the required documents and record working processes to demonstrate compliance. Nonconformities are eliminated by implementing corrective actions. (International Organization for Standardization, 2017)

ISO 13485 encourages the manufacturer to follow process approach by implementing the Plan-Do-Check-Act (PDCA) cycle and risk-based approaches. The PDCA cycle consists of four phases. The Plan phase establishes the objectives and resources for the process and identifies requirements and risks. In the Do phase the plan is implemented. In the Check phase processes are monitored and measured against the requirements and results are reported. In the Act phase the performance is maintained and improved. Risk-based approach identifies the risks that could prevent the manufacturer processes from reaching the desired results and minimises the negative effects of these risks for the processes. (International Organization for Standardization, 2017)

Certification is the formal recognition by others that the QMS is compliant with regulatory requirements. Certification of ISO 13485 is not mandatory for medical device manufacturers, but it can be a beneficial marketing point. Some customers can require certification and competitors could provide certified services. ISO 13485 is certified when a formal audit by a certification body is approved. (International Organization for Standardization, 2017)

ISO 14971 guides on the risk management of medical devices. The standard guides the manufacturer to implement a risk management plan, detailing the risk analysis process, competent personnel and criteria for risk or residual risk acceptability. The manufacturer must first identify the reasonably foreseeable misuses and other characteristics of the device related to safety. Then the manufacturer can identify hazards, hazardous situations and possible harm to patient based on these device characteristics. The probability of occurrence of harm and severity of the harm are estimated, and possible control measures are implemented. If the benefits of the intended use of the device outweigh the residual risk, the risk can be determined as acceptable. If the risks are greater than the benefits, new control measures are considered or the device or its intended use must be modified. All reported risks must be found in the risk management file, which is updated and reviewed regularly by the manufacturer. The risks of medical devices and IVD medical devices are inherently

different. Medical device risks are often related to the direct contact between the device and the patient. IVD medical device risks are more often related to the impact on patient management, because IVD tests often influence the diagnostic decision and patient management of the clinician. An incorrect result poses the greatest risk associated with IVD medical devices. (The International Organization for Standardization, 2019; Global Harmonization Task Force, 2012)

European Commission (2020) Implementing Decision (EU) *2020/439 of 24 March 2020 on the harmonised standards for in vitro diagnostic medical devices drafted in support of Directive 98/79/EC of the European Parliament and of the Council* lists the harmonised standards of the IVDD. Even though the directive is repealed by the IVDR, a common expectation is that the same standards should also be followed under the IVDR. There will likely be updated versions of ISO standards that will be harmonised with the IVDR in the future. On the 19th of July 2021 the EU commission notified about four ISO standards related to sterilisation of health care products that will be harmonised with the IVDR. (European Commission, 2021a) EU 2020/439 states that the requirements for IVD device in Directive 98/79/EC are different from IVDR 2017/746 and the standards harmonised to Directive 98/79/EC should not be used to demonstrate conformity with the IVDR (European Commission, 2020). However, many of the directive harmonised standards are identified to be important tools in demonstrating conformity with the IVDR (Dagher et al., 2019).

Medical Device Single Audit Program (MDSAP) founded in 2012 allows manufacturers of medical devices of member countries to be audited by recognised auditing organisations to avoid other regular audits in these countries. The members are Therapeutic Goods Administration of Australia, Brazil's Agência Nacional de Vigilância Sanitária, Health Canada, Japan's Ministry of Health, Labour and Welfare, and the Japanese Pharmaceuticals and Medical Devices Agency and the FDA. ISO 13485 is covered by this program. (Unites States Food and Drug Administration, 2021)

The IMDRF consists of voluntary medical device regulators from around the world who have defined Global Harmonisation Task Force (GHTF) on Medical Devices. The

IMDRF provides assistance for regulation and standard harmonisation in countries where medical device regulation is minimal. The Asian Harmonisation Working Party and Asia-Pacific Economic Cooperation are advocates of harmonising standards in Asia. The Pan African Harmonisation Working Party, the East African Community, Nigeria, and South Africa are advocating for the beginning of regional harmonisation of medical device regulations in Africa. According to Schuh & Funk (2019), harmonising standards in Latin America has not been prioritised. American National Standards Institute provides voluntary guidelines to in the US and medical device safety testing is standardised by the Good Laboratory Practices. The WHO provides a global regulatory framework for medical devices, which is based on the GHTF. (Schuh & Funk, 2019)

3.2 Medical device software standards

In addition to general medical device standards, there are standards that are applied to software in medical devices and software that is itself a medical device. International Electrotechnical Commission IEC 62304:2006 *Medical device software — Software life cycle processes* addresses the life cycle requirements for medical device software. The standard gives guidance on the development process, software maintenance, problem resolution and configuration management on software devices and requires using ISO 14971 for risk management. The standard provides additions to ISO 14971 with software specific risk classifications and guidance on decomposing the software based on the risk class. IEC 62304 software safety classes A, B and C should not be confused with the MDR or the IVDR risk classification. IEC/TR 80002-1:2009 *Medical device software – Part 1: Guidance on the application of ISO 14971 to medical device software* also provides supporting information to applying ISO 14971 in software context. (Bianchini et al., 2019; International Electrotechnical Commission, 2015)

IEC 82304-1:2016 *Health software — Part 1: General requirements for product safety* addresses the safety requirements for software used in health applications on a

product level supporting the scope of IEC 62304. IEC 82304 specifies on software product requirements, validation, identification, instructions provided with the device and post-market activities. IEC 60601-1 *Medical electrical equipment — Part 1-11: General requirements for basic safety and essential performance* addresses programmable electrical medical systems and requirements on networks and software interfaces. (Bianchini et al., 2019)

4 Regulatory requirements

Medical devices and IVDMD are qualified as such based on the intended use set by the manufacturer. The manufacturer must be able to demonstrate the safety and effectiveness of the device in the intended conditions of use. The regulatory control of the devices is proportional to the risk that can stem for using the device. (Thorogood et al., 2018) This chapter discusses the regulatory requirements of medical devices and IVDMDs in Europe and globally.

4.1 IVDR and MDR

In 2012, European Commission released a press release about tightening controls and increasing surveillance of medical devices, to restore confidence in medical device safety. The reason for this call action was a French manufacturer, Poly Implant Prothèse (PIP), that had used industrial silicone instead of medical grade silicone in breast implants. The call to action included determining that more medical devices would be audited by external notified bodies and a notified body can audit only medical devices in their area of expertise. Other actions highlighted were the reinforcement of market surveillance, improvement of vigilance systems, and ensuring traceability by implementing Unique Device Identification system. (European Commission, 2012a) In 2012, the PIP Action Plan addressing the issues was launched. The plan led to the preparation of the MDR 2017/745 and the IVDR 2017/746. (European Commission, 2012b)

Medical devices are controlled under 2017/745 Medical device regulation (MDR). This regulation amends Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repeals Council Directives 90/385/EEC and 93/42/EEC. The transition period for economic operators to follow the MDR ended on 25th of May 2021. *In vitro* diagnostic medical devices are regulated by 2017/746 in Europe after the transition period ends in May 2022. This regulation repeals Directive

98/79/EC and Commission Decision 2010/227/EU. The motive for these new regulations is to ensure safety and quality of the product and monitoring the performance of the product even after placing it on the market. The regulations emphasise risk-based evaluation and verification of the clinical and analytical performance. Certain certificates of devices under the MDD, the Active Implantable Medical Devices Directive (AIMDD) or the IVDD can be valid until 2024 if major changes are not done to the device. Major changes include change in intended use, new therapeutic or diagnostic features and changes in databases or product architecture. However, even for these legacy products, the post-market surveillance, market surveillance, vigilance, and registration of economic operators and of devices must be compliant with the new regulation withing the transition period. (European Parliament & Council of the European Union, 2017a; 2017b; Dagher et al., 2019; Medical Device Coordination Group, 2020a)

A software used alone or in combination with a medical device or an IVDMD is classified as a medical device or an IVDMD when it is used for a medical purpose. Mobile apps with a medical purpose are classified as medical devices. (Thorogood et al., 2018) The IVDR includes software that is for example used in genetic testing, to make diagnosis or interpretation of genome for a medical purpose. Claimed benefits and safety should be ensured by following the regulation. However, genetic ancestry or paternity tests are not regulated under the IVDR. (Dagher et al., 2019)

The requirements of the MDR and the IVDR are mainly similar. The IVDR contains 113 articles and 15 annexes, The MDR contains 123 articles and 17 annexes. The articles are divided into ten chapters in both regulations. The annexes provide additional information on the requirements presented in the articles. Both regulations start with chapter I, containing scope and definitions and regulatory status of products. Chapter II describes placing devices on the market and putting them into service, obligations of economic operators, CE-marking and free movement on the market. Chapter III presents identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, and

European database on medical devices (EUDAMED). Chapter IV contains the requirements for notified bodies. Chapter V contains information on device classification and conformity assessment. In the MDR, chapter VI describes the requirements for clinical evaluation and clinical investigations, and correspondingly in the IVDR, the chapter describes the requirements for clinical evidence, performance evaluation and performance studies. Chapter VII presents post-market surveillance, vigilance and market surveillance requirements. Chapter VIII discusses cooperation between member states, medical device coordination group (MDCG), expert laboratories, expert panels and device registers. Chapter IX describes confidentiality, data protection, funding and penalties related to the regulations. Chapter X contains final provisions on how the regulations will be entered into force. (European Parliament & Council of the European Union, 2017a; 2017b)

Article 10, General obligations of manufacturers in chapter II compiles the most important requirements for a manufacturer. A QMS is one of the key requirements presented in the article. All manufacturers regardless of the device risk classification must have a QMS that is continuously improved and updated. Manufacturers can develop their QMS to be proportionate to the risk class and the type of devices. The QMS must include a strategy for regulatory compliance, addressing applicable general safety and performance requirements, responsibility of the management, resource management including management of suppliers and sub-contractors, risk management, performance evaluation including post-market performance follow-up, product realisation including planning, design, development, production and service provision, assigning Unique Device Identification (UDI), setting-up a post-market surveillance system, handling communication with authorities, notified bodies, other economic operators, customers and other stakeholders, processes for reporting of serious incidents and field safety corrective actions in the context of vigilance, management of corrective and preventive actions, processes for monitoring and measurement of output, data analysis and product improvement. (European Parliament & Council of the European Union, 2017a; 2017b)

The UDI is a series of numbers of alphanumeric characters that are intended for the traceability of medical devices. UDI comprises of a UDI device identifier (UDI-DI) which identifies the device type and a UDI production identifier (UDI-PI) which identifies the unit of device production e.g. serial number or lot number. Additionally, Basic UDI-DI is used when device information is registered to the EUDAMED database. The UDI is implemented to the device and on the package in Automated Identification for Data Capture (AIDC) and human readable interpretation (HRI) forms. Software products have additional rules for issuing the UDI. Only HRI potion of the UDI is required in electronic displays of the software. A new UDI-DI is needed if the intended use, interpretation of data or original performance of the software is changed. New UDI-PI is required for minor software changes. (European Parliament & Council of the European Union, 2017a; 2017b)

Table 2 presents the topics of the annexes of the IVDR and the MDR.

Table 2. The annexes of the IVDR and the MDR (European Parliament & Council of the European Union, 2017a; 2017b).

The MDR	**The IVDR**
I: General safety and performance requirements	I: General safety and performance requirements
II: Technical documentation	II: Technical documentation
III: Technical documentation on post-market surveillance	III: Technical documentation on post-market surveillance
IV: EU declaration of conformity	IV: EU declaration of conformity
V: CE marking of conformity	V: CE marking of conformity
VI: Information to be submitted upon the registration of devices and economic operators in accordance with Articles 29(4) and 31; core data elements to be provided to the UDI database together with the UDI-DI in accordance with Articles 28 and 29; and the UDI system	VI: Information to be submitted upon the registration of devices and economic operators in accordance with Articles 26(3) and 28, core data elements to be provided to the UDI database together with the UDI-DI in accordance with Articles 25 and 26 and the UDI system
VII: Requirements to be met by notified bodies	VII: Requirements to be met by notified bodies

The MDR	The IVDR
VIII: Classification rules	VIII: Classification rules
IX: Conformity assessment based on a quality management system and assessment of the technical documentation	IX: Conformity assessment based on a quality management system and assessment of the technical documentation
X: Conformity assessment based on type examination	X: Conformity assessment based on type examination
XI: Conformity assessment based on product conformity verification	XI: Conformity assessment based on production quality assurance
XII: Certificates issued by a notified body	XII: Certificates issued by a notified body
XIII: Procedure for custom-made devices	XIII: Performance evaluation, performance studies and post-market performance follow-up
XIV: Clinical evaluation and post-market clinical follow-up	XIV: Interventional clinical performance studies and certain other performance studies
XV: Clinical investigations	XV: Correlation table
XVI: List of groups of products without an intended medical purpose referred to in Article 1(2)	
XVII: Correlation table	

Annex I of the regulations describes the general safety and performance requirements. The medical device must be designed and manufactured so that the device functions as the intended purpose states. Customers need to be notified about safety. If the device is used according to manufacturer's instructions, the health or safety of the patient should not be adversely affected. The information to be included into device labels and instructions are detailed in this annex. Instructions for use of the device must be delivered to customers, in professional use electronic manual is enough. Annex I describes the risk management system required from the manufacturer. It includes risk management plan which identifies the known and foreseeable hazards in the device and its use, addresses eliminating or controlling risks, evaluating associated risks, the overall risk, the benefit-risk ratio and risk acceptability. Annex I also contains general requirements related to different types

of medical devices, for example chemical, physical and biological properties, measuring functions, radiation, and software. For devices that incorporate software or for software that are devices in themselves, the development life cycle and risk management should consider the state of the art. (European Parliament & Council of the European Union, 2017a; 2017b)

Annexes II and III of the regulations focus on technical documentation. The technical documentation includes general information supplied by the manufacturer, general safety and performance requirements, benefit-risk analysis and risk management, product verification and validation (Annex II) and technical documentation on post-market surveillance (Annex III) and the post-market surveillance plan according to Article 79. The technical documentation is assessed by notified bodies, excluding the devices belonging in the lowest risk class. (European Parliament & Council of the European Union, 2017a; 2017b)

Annexes IV and V of the regulations describe the content of declaration of conformity and how the CE-mark is applied to devices. Annex VI outlines what information related to the device and the economic operated needs to be submitted when registering a medical device. This includes the UDI system intended to track of the economic operators and their devices. EU declaration of conformity and CE marking of conformity must be done by all economic operations to confirm that the requirements of the regulation have been fulfilled. (European Parliament & Council of the European Union, 2017a; 2017b)

Annex VII of the regulations identifies the requirements needed to be fulfilled by the notified bodies. Notified bodies need to have their own QMS. There are also requirements for notified body's resources and competence of personnel. The annex also outlines what the audits conducted by notified bodies include and how the results are reported. Annex XII outlines the certificated that are issued by notified bodies related to conformity assessment of devices. (European Parliament & Council of the European Union, 2017a; 2017b)

Annex VIII of the regulations contains device classification rules. The IVDD 98/79/EC allowed manufacturers to self-certify most devices now falling under the IVDR. Under the directive, the classification was based on risks: high risk IVD devices included in list A of the directive, moderate risk IVD devices included into list B of the directive and low risk IVD devices. High risk IVD devices include reagent products intended for determining blood groups or detecting human T-lymphotropic virus, hepatitis or human immunodeficiency virus. Moderate risk IVD devices include for example reagent products that detect infections, antibodies, certain tissue types and tumoral markers. Self-testing products, for example devices for measuring blood sugar levels are included into the moderate risk IVD devices. Low risk IVD devices are other IVD devices that are not included into the higher risk groups. Low risk devices under the IVDD are self-evaluated by the manufacturer, higher risk devices are evaluated by notified bodies to obtain the CE-mark for the product. (European Parliament & Council of the European Union, 1998)

Deviating from the IVDD, the IVDR classifies devices from A to D. Class D devices have the highest risk level and Class A devices have lowest risk level. Class A devices can be self-assessed and certified by the manufacturer. Class B, C and D are assessed by notified bodies. (European Parliament & Council of the European Union, 2017b) According to an analysis of IVD classifications in The Netherlands, a substantial amount of IVDs are considered to belong to a higher risk class under the IVDR than under the IVDD. Under the IVDD 7% of IVDs required assessment from notified bodies. Under the IVDR 84% of IVDs in The Netherlands belong to classes B to D and require assessment from notified bodies. (Van Drongelen et al., 2018) Table 3 presents a summary of device classification under the IVDR.

Table 3. The IVDR classification system (Medical Device Coordination Group, 2020b).

Classification	Description of devices
Class D	Devices intended for the detection of a transmissible agent in blood, blood components, cells, tissues or organs, for assessing their suitability for transfusion, transplantation or cell administration. Devices intended for the detection of a transmissible agent that causes a life-threatening disease with a high risk of propagation. Devices intended for determining the infectiousness of a life-threatening disease where monitoring is critical in patient management process. Devices intended for blood grouping.
Class C	Devices intended for blood grouping other than those intended to determine markers listed for class D. Devices intended for detecting a sexually transmitted agent. Devices intended for detecting of an infectious agent in cerebrospinal fluid or blood without a high risk of propagation. Devices intended for detecting of an infectious agent, if a life-threatening situation for the patient or for the individuals-offspring is possible. Devices intended for pre-natal screening to determine the immune status towards transmissible agents. Devices intended to be used as companion diagnostics. Devices intended for disease staging, where a life-threatening situation for the patient is possible. Devices intended to be used in screening, diagnosis, or staging of cancer. Devices intended for human genetic testing. Devices intended for monitoring of levels of medicinal products, substances or biological components, where a life-threatening situation for the patient is possible. Devices intended for management of suffering from a life-threatening disease or condition. Devices intended for screening for congenital disorders in the embryo or fetus. Devices intended for self-testing.
Class B	Devices for the detection of pregnancy, fertility testing, determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine.

Classification	Description of devices
Class B	Devices which are controls without a quantitative or qualitative assigned value. Devices not covered by the other classification rules.
Class A	Devices for general laboratory use, accessories with no critical characteristics, buffer solutions, washing solutions, general culture media and histological stains, intended for in vitro diagnostic procedures relating to a specific examination. Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures.

Under the MDD 93/42/EEC and the MDR, medical devices are classified to classes I, IIa, IIb and III, class I being the lowest risk class and III the highest. Class I devices can be self-assessed and certified by the manufacturer. Class IIa, IIb and III are assessed by notified bodies under the MDR. Devices under class I are non-invasive, and the risk associated with the use of the device is low. Class II devices are classified under two sub-classes: IIa and IIb. Class IIa devices are invasive devices for short term use and class IIb are invasive devices for long term use. Devices in class III have high risk for the patient or the user. These are commonly implantable devices that are invasive, for example devices that come into contact with the central nervous system. (European Parliament & Council of the European Union, 2017a) Examples of the MDR classification are given in Table 4.

Table 4. The MDR classification system (European Parliament & Council of the European Union, 2017a).

Classification	Description of devices
Class III	Non-invasive devices consisting of substances intended to be used *in vitro* in direct contact with human cells, tissues or organs taken from the human body or used *in vitro* with human embryos before their implantation or administration into the body. Active devices intended for controlling, monitoring or directly influencing the performance of active implantable devices. Devices incorporating a substance which, if used separately, can be considered as a medicinal product. Devices manufactured utilising tissues or cells of human or animal origin, or their derivatives, which are non-viable. Active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as closed loop systems or automated external defibrillators.
Class IIb	Non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other liquids intended for implantation or administration into the body. Invasive devices intended for long-term use. Implantable devices and long-term surgically invasive devices. Active devices intended to control or monitor the performance of active therapeutic class IIb devices. Active devices intended to emit ionizing radiation for therapeutic purposes. Active devices intended to administer and/or remove medicinal products, body liquids or other substances to or from the body, unless there is a potential hazard for the patient. Devices used for contraception or prevention of the transmission of sexually transmitted diseases.
Class IIa	Non-invasive devices for channelling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of infusion, administration or introduction into the body. Invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to a class IIa, class IIb or class III active device. Invasive devices if they are intended for short-term use. Surgically invasive devices intended for transient use.

Classification	Description of devices
Class IIa	Active therapeutic devices intended to administer or exchange energy. Active devices intended for diagnosis and monitoring. Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes. Devices specifically intended for recording of diagnostic images generated by X-ray radiation.
Class I	Non-invasive devices. Invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device. Active devices not covered by other rules.

Annexes IX, X and XI of the regulations describe the methods of conformity assessment of the regulatory requirements. There are different options which an economic operator can choose for their conformity assessment. First option is the assessment of quality management system and technical documentation according to Annex IX. Another option is the type examination according to Annex X combined with production quality assurance according to Annex XI part A. The third option is to combine the type examination according to Annex X with product verification according to Annex XI part B. Differently classified devices have different requirements for the assessment. Class I (MDR) and class A (IVDR) devices do not need to be assessed by a notified body, the economic operators can self-assess these devices by writing technical documentation according to annexes II and III. Additionally, custom made devices are assessed according to instructions in Annex XIII of the MDR. (European Parliament & Council of the European Union, 2017a; 2017b)

For the MDR, Annex XIV describes requirements for clinical evaluation and post-market clinical follow-up. Annex XV describes clinical investigations. Similarly, in the IVDR, Annex XIII describes performance evaluation and post-market performance follow-up and Annex XIV describes clinical performance studies. Manufacturers are

required to plan and execute clinical/performance studies for their devices. They also need to plan and implement a process for collecting data of the device after it has been placed to the market. Performance evaluation demonstrates the scientific validity, analytical performance and clinical performance of the device. The content of performance evaluation plan is described in Annex XIII. It includes for example evaluation general safety and performance requirements that require support from relevant scientific validity and analytical and clinical performance data, description of the state of art, data sources used for decision making and evaluation of the benefit-risk ratio for the intended purpose. Demonstration of the performance is shown in analytical performance report, clinical performance report, scientific validity report and an assessment of those reports allowing demonstration of the clinical evidence. Clinical performance studies are performed based on a clinical performance study plan. (European Parliament & Council of the European Union, 2017a; 2017b) The new regulations in Europe bring especially the IVDMD requirements closer to the regulations in the United States in terms of the requirements for clinical validation. The new regulations better support the safety and performance of devices which is beneficial for the patients. (European Parliament & Council of the European Union, 2017a; 2017b; Dagher et al., 2019)

Annex XVI of the MDR lists products without an intended medical purpose that are regulated under the MDR. These products include for example contact lenses and high intensity electromagnetic radiation emitting equipment intended for use on the human body. Finally, the last annex of both regulations lists correlation between the articles of previous directives and the current regulations. The MDR is compared to Directive 90/385/EEC and Directive 93/42/EEC and the IVDR is compared to Directive 98/79/EC. (European Parliament & Council of the European Union, 2017a; 2017b)

The MDR and the IVDR obligate the organisation to name a person responsible for regulatory compliance. This person must have relevant education degree and at least one year of experience in regulatory affairs or QMS relating to medical devices or IVD medical devices, or in absence of education degree, four years of professional

experience. This person is responsible for conformity of devices and the QMS, technical documentation, EU declaration of conformity, post-market surveillance, reporting and performance studies or clinical studies. Micro and small enterprises are not required to have a person responsible for regulatory compliance withing the organisation but are still required to appoint this person. (European Parliament & Council of the European Union, 2017a; 2017b)

4.2 Global regulations

An economic operator must take into account the regional regulations and law in the places they manufacture, distribute or sell medical devices. The IMDRF develops guiding documents for medical device regulation. Members of the IMDRF are Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the USA. The IMDRF (GHTF) has defined guidance on the risk-based approach on risk classification which influences the regulatory framework of many countries and areas globally. (Kedwani et al., 2019)

The FDA regulates medical devices in the U.S. market under the Federal Food Drug and Cosmetic Act since 1938. The FDA classifies medical devices to risk classes I, II and III, where class I contains low risk devices with minimal potential to harm, class II contains medium risk devices and class III contains high risk devices that are implantable, support life or present potential unreasonable risk of injury. Class I and II devices often require Premarket Notification 510(k) sent to FDA so that the device can legally be marketed as safe and effective. Class III devices require Premarket Approval by the FDA, which is more stringent than 510(k). Valid scientific evidence mut be provided to FDA demonstrating the safety and effectiveness of the device. After the approval of the premarket submission, the device must comply with regulatory controls of the relevant risk class and establish registration and device listing. In the U.S., NGS technologies are often classified as laboratory-developed tests (LDTs). LDTs are IVDMDs that are designed and manufactured to be used in a single laboratory. Only a portion of systems using NGS technologies, often cancer

panels, go through the FDA approval for medical devices. In the future FDA is likely to be more involved in the regulation of LDTs. (United States Food & Drug Administration, 2020; Lamph, 2012; Thorogood et al., 2018)

Health Canada reinforces regulations in Canada. Canada is part of the Medical Device Single Audit Program (MDSAP), which means that all medical device manufacturers operating in Canada must certify their quality management system through the MDSAP. (Kedwani et al., 2019) Health Canada classifies medical devices to risk classes I, II, III, and IV, where class I devices have low risk and class IV devices have high risk. Class I devices do not require medical device license, which is required from the devices in other classes. Devices in classes II, III and IV need to also comply with quality management system requirements of Health Canada. (Thorogood et al., 2018) In Mexico, the regulations are based in EU regulations and the FDA regulations (Kale, 2019). In Brazil, the Brazilian Health Regulatory Agency categorises medical devices to medical equipment, materials for health use, orthopedic implants and IVDs. Medical devices are classified to risk classes I, II, III and IV. (Brazilian Health Regulatory Agency, 2020)

In Asia, the Association of Southeast Asian Nations (ASEAN) have implemented a medical device directive (AMDD) to harmonise regulatory requirements in Asia. Members of the ASEAN are Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam. (Kedwani et al., 2019) Indian medical device regulation from 2018 divides the devices to risk classes A, B, C, and D, where devices in class A have lowest risk and devices in class D have highest risk. The classification is influenced by GHTF guidance. (Kale, 2019)

in Australia, the Australian Therapeutic Goods Administration is responsible for medical device and IVD regulation. The regulations consist of pre-market assessment of the devices, market authorisation and post-market monitoring. Medical devices are classified based on their risk to classes I, II, III and Active Implantable Medical Devices (AIMD), where class III devices and AIMDs have the highest risk associated with them. IVD devices are classified based on public health risk associated with the

device. The classes are 1, 2, 3 and 4, where devices in class 4 have high public health risk. (Australian Government, Therapeutic Goods Administration, 2020)

In developing countries, the challenges related to medical device regulation are often due to the policymakers' lack of understanding of the industry and the lack of resources (Kale, 2019). In some of African countries, there is a limited access to medical devices and IVD devices. There is a lack of common regulations across the continent, but local regulations are reinforced by national regulatory authorities. (Kedwani et al., 2019) In Egypt, the Egyptian Ministry of Health is regulating medical devices. Egypt uses the European MDD 93/42/EEC as the basis of defining and classifying medical devices. Similarly, Kenya uses GHTF recommendations and European directives MDD 93/42/EEC, AIMDD 90/385/EEC and IVDD 98/79/EC as their regulatory framework. South Africa does not have well-defined regulation system, but FDA approved or CE-marked products are preferred on the market. (De Maria et al., 2018)

In Finland, there are two laws related to medical devices, the act on medical devices 719/2021 and the act on certain healthcare devices and applications 629/2010 that complement the MDR, the IVDR and directives still applying to medical devices under the IVDD and the AIMDD. The certain healthcare devices in the 629/2010 law name refer to IVDs under the IVDD 98/79/EC and AIMDs under the AIMDD 90/385/EEC. These laws describe e.g. additional requirements for economic operators, clinical studies and performance evaluation, vigilance and surveillance payments to Finnish Medicines Agency. (Finlex 2021, Finlex 2010)

5 QMS framework for variant interpretation software

This chapter synthesises the chapters 2 to 4 on product development, medical device standards and regulatory requirements and applies them in the context of variant interpretation software to outline the framework for a quality management system. OmnomicsNGS is a tertiary analysis tool for NGS variant interpretation and reporting provided by Euformatics Oy located in Finland. OmnomicsNGS is meant for biologists, clinicians and geneticists to search and combine patient sequenced DNA variants with information from public databases including ClinVar, CIViC, Ensembl, HPO, OMIM etc. The analysis tool is compatible with any sequencer and kit used by clinicians and can be used from the cloud or installed to customer premises to ensure patient data safety. OmnomicsNGS is integrable into electronic patient record systems and laboratory information management systems. The information omnomicsNGS user can find related to patient variants include which gene the variant is in, description of genes, drugs targeting these genes and the association of variants and genes to diseases. OmnomicsNGS allows clinicians to filter and classify variants and generate genetic or oncology reports based on ACMG/AMP/ASCO/CAP criteria. Quality control metrics including coverage analysis are automatically included to the reports created by users. The aim of Euformatics is to provide omnomicsNGS as a IVDR compliant software. OmnomicsNGS is classified as an IVD software because it provides information about human genome and can be used by a clinician to help guide diagnosis or treatment options. (Euformatics, 2021)

It is mandatory for an IVDMD manufacturer in Europe to comply with the IVDR, starting form 26th of May 2022. The requirement includes the implementation of a QMS. Even though the certification of standards is not mandatory, non-conformances to common medical device standards may affect the performance of the product on the market. Standards provide valuable requirements on device safety, traceability and usability and can give detailed descriptions of processes related to the product of the QMS. Applying with standards is seen as a presumption

of conformity to regulations. (Bianchini et al., 2019) This thesis aims to answer the questions of what the minimum requirements are for implementing a quality management system that is not too laborious for a manufacturer to maintain and is simultaneously beneficial in terms of marketing and sales. Euformatics also wishes to continue with agile software development process during the IVDR compliance.

There are currently no clear instructions, whether genetic variant database software is classified under the MDR or the IVDR. As sequencing machinery is regulated under the IVDR, it could be considered that the genetic variant database software use to interpret sequencing results is also regulated under the IVDR. According to MEDDEV 2.1/6 guidance document, software that "integrates genotype of multiple genes to predict risk of developing a disease or medical condition" is considered as an IVDMD. MDCG 2019-11 defines that a software which uses information solely obtained from an IVDMD is regulated under the IVDR. The guidance document gives an example of a medical device software that is used to predict risk of a disease or a medical condition by integrating genotypes, which would be classified under the IVDR independently of any other device. Uncertainty of the applying regulations and classification rules can discourage the development of software with a medical purpose. This uncertainty can slow down the innovation of diagnostics and treatment methods. (Thorogood et al., 2018; Medical Device Coordination Group, 2019)

The IMDRF has defined guidance on the risk-based approach on risk classification that includes software. In the contexts of medical device software, the software is considered to belong to a high risk class if the information provided by the software is used to diagnose or make immediate or near term actions of treatment. If the software is used to aid in diagnosis or treatment, the software is considered to belong to a medium risk class. The software is classified as low risk class if it only informs of treatment or diagnosis options and does not result in any immediate actions. However, the risk-based approach to classification is only suggestive guidance and areal differences in classification rules are found. For example, all devices intended for genetic testing belong to class C under the IVDR. It is unclear, does the intended

use determined by the manufacturer affect the classification of software if the software only aids diagnosis or informs diagnosis options. Guidance form regulatory authorities is still required in these kind of specific classification questions. (Thorogood et al., 2018)

The aim of Euformatics' software development process is to combine agile software development with complying with regulatory requirements. Euformatics has been using Scrum as the software development method and quickly meeting customer requirements continues to be a high priority of the company. The objective of the thesis for software development perspective is to recognise the gaps between the current Scrum development process and a development process compliant with ISO 13485 and the IVDR while still maintaining the ability of the company to rapidly respond to the product requirements of customers.

Complying with the QMS and producing appropriate records will cause additional burden for the company. The company is interested in what kind of effects the QMS has on the company and if the QMS will slow down the software release process. Although the QMS will obligate the company to implement new processes including management reviews and internal audits, it is hypothesised that these processes do not directly affect the software release schedule. This thesis will discuss the effects of ISO 13485 product realisation, measurement, analysis and improvement requirements, ISO 14971 risk management, IEC 62304 software life cycle management and IEC 62366-1 usability engineering requirements on the release process. Figure 6 presents these critical processes in the context of software manufacturer functioning under the IVDR framework.

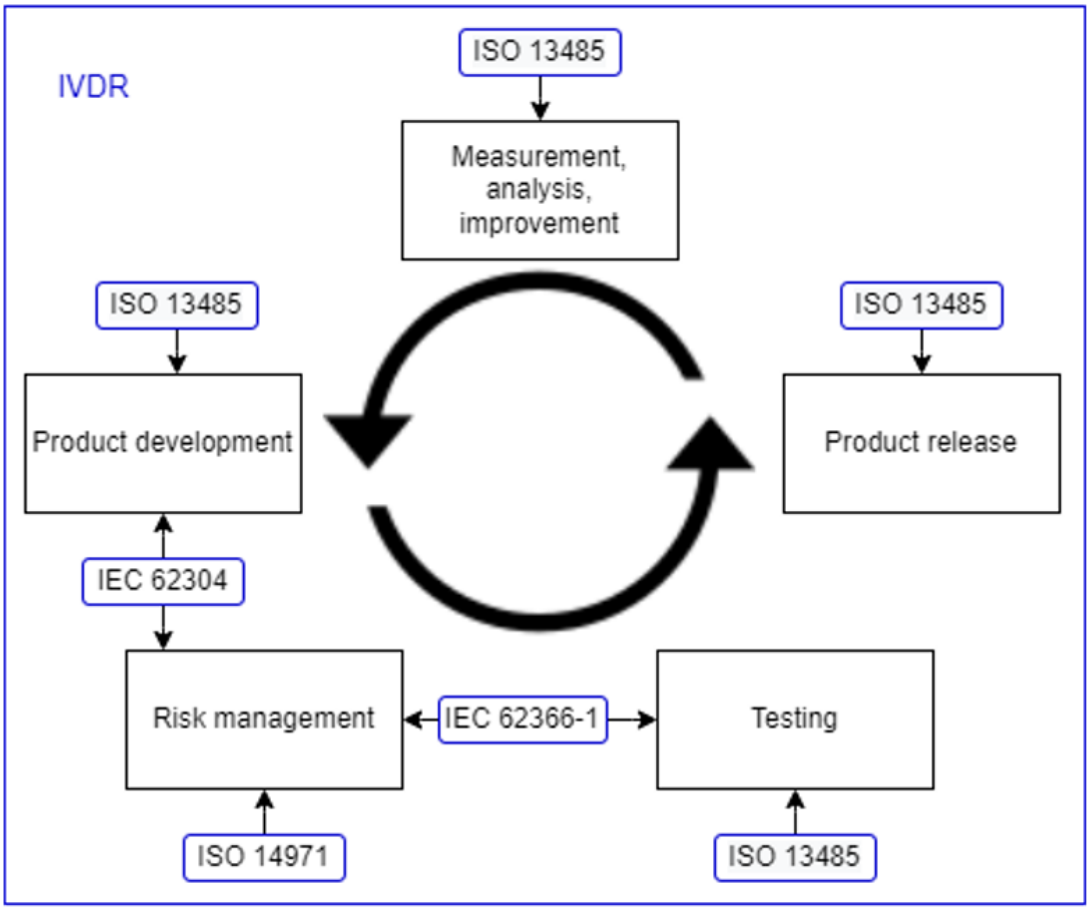

Figure 6. Critical steps in the software development process in the context of the IVDR and medical device standards.

6 Research process, data and methods

The research process consists of two parts: Interviews with medical device manufacturers and action research to develop the quality management system based on a literature review and the requirements of the organisation developing the genetic software tool. The methods and collection of data are described in this chapter.

6.1 Interviews

Interviewing is a common research method to acquire qualitative data about a topic or an experience. An interview can be unstructured, semi-structured or structured. Structured interviews have a predefined questions and often very specific answers are expected. The questions are seldom open-ended. Unstructured interviews do not have any pre-set questions and can be based on observations arising from the conversation. (DiCicco-Bloom & Crabtree, 2006; DeJonckheere & Vaughn, 2019)

Semi-structured interviews are often used in qualitative research. These interviews have often a set of open-ended questions but also include questions and topics arising from the conversation. Semi-structured interviews follow a basic research question, so that the interviewees can be selected based on their knowledge on the research topic. 5-10 more specific questions are often developed by the interviewer to support the basic research question. During the interview, questions can be dopped and new ones added based on the interviewee's expertise and interests. (DiCicco-Bloom & Crabtree, 2006)

Semi-structured interview plan was modified from DeJonckheere & Vaughn (2019). The first step is to determine the purpose and scope of the study. The research question identified for the study was *How are other medical device companies developing their QMS to comply with the IVDR or the MDR?* The scope of the study

was identified as 5-10 Finnish medical device companies. Secondly, the participants were identified. The participants must be knowledgeable on developing the QMS and the company must be planning to make the transition to comply with the MDR or the IVDR or already comply with new regulations. Software companies with medical device or IVDMD products were also a group of interest when identifying participants. Quality Managers of Finnish medical device or IVDMD companies were contacted, and the prerequisites of the study were explained to the possible participants with a research handout containing information on the research and handing of information.

It is important to consider ethical issues when interviewing private companies. Some of the interviewed companies may be competing with Euformatics if their business is related to NGS. In these cases, it was considered that the possible conflicts of interesses were communicated with the participant and no compromising questions were asked in the interview. All companies and interviewees are kept anonymous to protect possible sensitive information and competitiveness of the companies. The sensitive nature of the topic of the interview can limit the amount of useful information acquired from the interviews.

The next step in the interview process was to develop the guiding questions for the interview. The guiding questions are presented in Appendix 1. The interview questions were modified during the interviews based on the company's products and the regulatory compliance. The companies that are already compliant with the regulation can be expected to have definite information of their QMS processes whereas the companies with a plan to develop a regulatory compliant QMS may not yet have found their solution for all QMS processes. The plan was to conduct the interviews between April and June of 2021. The findings of the interviews are presented in Chapter 8.

6.2 Methods for quality management system development

Action research in organisation development is based on the collaboration of scientific research and organisational requirements. The objective of action research is to develop an action plan and implement it based on scientific research to solve a problem an organisation is facing. Action research aims to develop organisational projects and increase the scientific knowledge behind these processes within the organisation. (Coghlan & Shani, 2014)

One key concept of action research is to determine the purpose, rationale, and context of the research. The organisation must determine why the project is worth developing and implementing. The organisation must also consider the research in the business, social and academic contexts. These contexts provide requirements for the project and outlines the personnel included in the development and reflection of research relating to the project. (Coghlan & Shani, 2014)

Another key concept of action research is to define the methodology of actions (Coghlan & Shani, 2014). The quality management system starts with planning. The inputs identified for the QMS plan were organisation goals aiming to certify the IVDMD, meeting regulatory requirements of the IVDR and ISO 13485. ISO/TC 210 Practical guide recommends using the concept of a PDCA cycle as the method to develop and implement the QMS. The outputs of the QMS plan according to the practical guide are gap analyses, action plans, the quality manual and other QMS documentation. (International Organization for Standardization, 2017)

Basler & Pizinger (2004) determine gap analysis as the first step of implementing ISO 13485. Research conducted by Bujok et al. (2017) found that gap analysis done to find the non-compliant areas of the QMS is the first step to in obtaining the CE mark. Gap analysis aims to identify the current situation of the QMS documents in the organisation, the regulatory requirements and the gap between the current situation and regulatory compliance. The analysis and the design of the QMS are based on scientific literature. Expert consultations can also be used to plan for implementation

of regulatory compliant processes. The MDCG offers guidance documents on compliance with EU regulations for medical devices. Based on the gap analysis, an action plan for implementing the QMS can be developed. The plan should consist of practical actions that can be completed to reach the identified gaps. The responsibilities of each task should be assigned to person in charge of the process area. (Basler & Pizinger, 2004; Bujok et al., 2017; Coghlan & Shani, 2014) For a more detailed action plan, an initial model for the quality system was created based on the literature review and the gap analysis. This model is presented in chapter 7.

The next step in the QMS process is to implement the action plan. The implementation includes writing, reviewing, and approving the new QMS documents and training the personnel on new procedures. After the QMS action plan is implemented, an internal audit should be conducted to gather evidence on compliance with the regulations. (Basler & Pizinger, 2004) The QMS will be verified by a notified body external audit. The verification of the implemented QMS through audit processes is out of the scope of this thesis.

The thesis presents the development and implementation of a QMS based on literature research and internal requirements of the company. Six people inside the company were identified to be able to participate in the writing process of QMS processes and other personnel was involved in conversations about the processes. Collaborative efforts inside the company combined with the literature research presented in the thesis were used to develop the processes to fit the agile software development process with the IVDR and ISO 13485 requirements.

7 Model of a hypothetical quality system

The hypothesis of the thesis was that literature research, interviews and collaboration inside the company could be combined with gap analysis and PDCA cycle to be utilised in developing an action plan and a strategy for implementation of the QMS.

The decision was made to first plan and implement the QMS according to ISO 13485 requirements. This choice was made by the company based on the information that ISO 13485 has been a harmonised standard under 98/79/EC and it is globally recognised in the IVDMD market. After the ISO 13485 QMS is implemented, the IVDR requirements and other standards could be implemented.

It is hypothesised that the QMS will benefit the company. Based on the literature research of the thesis, there were no indications that following regulatory requirements would negatively affect the company or the product. Implementing regulatory requirements might slow down the agile software development but when the design and development, user testing, and releasing processes of the product are documented and executed according to written documentation every time, and all features are traceable in the process, the safety and usability of the product will increase. It is also hypothesised that the QMS will help the product to compete in the marked as it can be used as a selling point.

7.1 Quality system structure

According to the ISO 13485, the quality manual is a document that outlines the structure of the QMS. The hypothetical structure of the QMS documentation is presented in Figure 7.

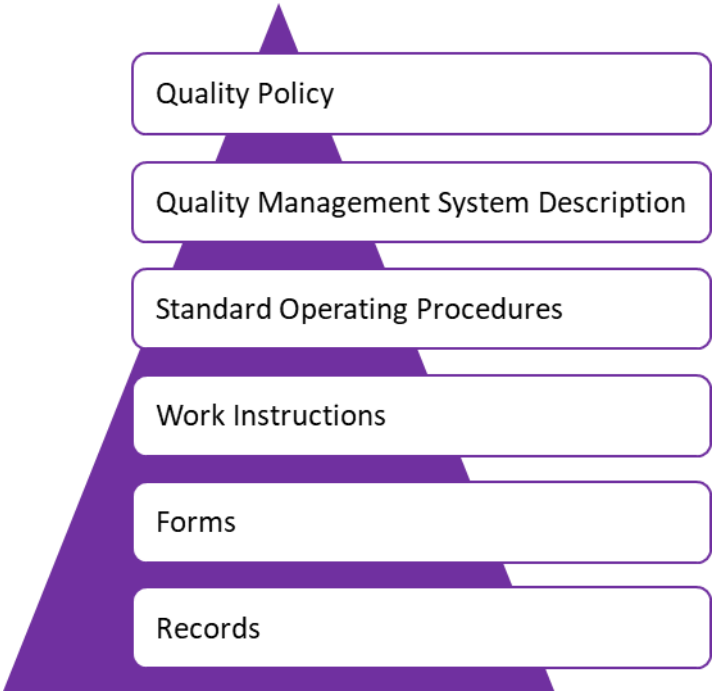

Figure 7. The structure of the quality management system documentation.

The structure of the QMS documentation is presented as a shape of a pyramid. At the top of the pyramid is the Quality Policy, which establishes the company's commitment to quality. Quality Management System Description established the structure of the QMS, the company processes and interactions of those processes. Together, the Quality Policy and Quality Management System Description are included into the Euformatics Quality Manual. The Quality Manual establishes the scope and structure of the QMS and justifies non-applicable sections of ISO 13485 and IVDR.

The next level of the QMS pyramid is Standard Operation Processes (SOP). SOPs describe the processes of the company established in the Quality Management System Description. The next level of the pyramid is Work Instructions. These documents are descriptions of the tasks needed to carry out SOPs. Under Work Instructions are Forms which are used to save information on performed processes. The bottom of the pyramid is Records. Records contain the saved information of processes and task to ensure traceability of the entire QMS.

The QMS quality manual should present the QMS processes and the relation between them. Figure 8 presents the hypothetical QMS of Euformatics based on core processes.

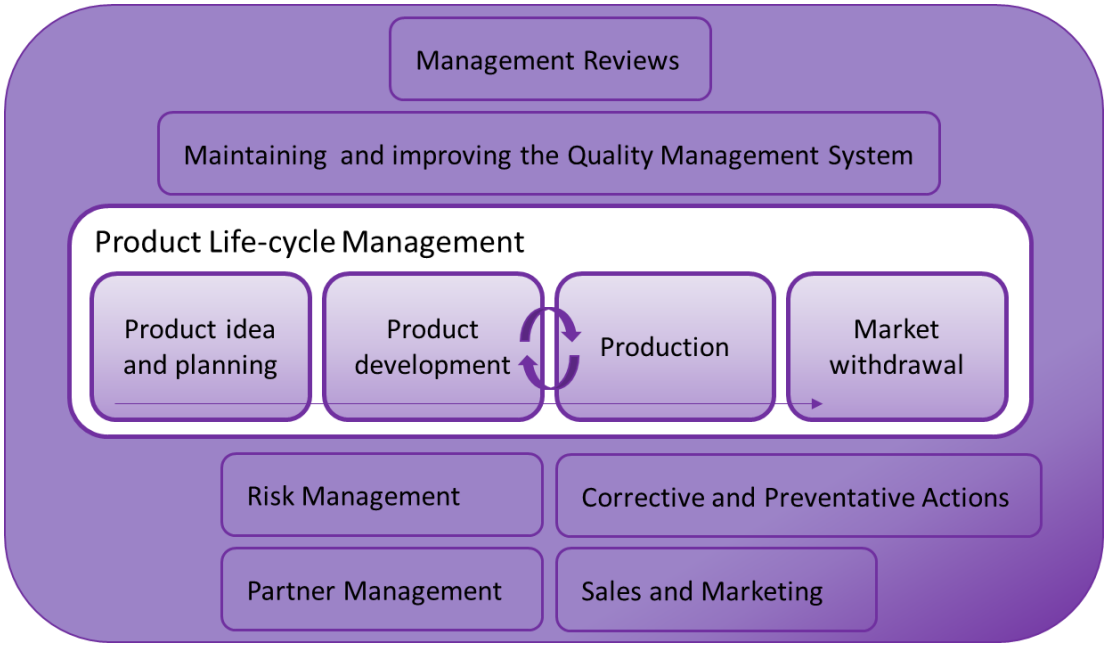

Figure 8. The quality processes of Euformatics.

Product life cycle management is the core of the Euformatics' operation. The life cycle of omnomicsNGS starts from the product idea and planning and progresses into product development and production. The life cycle also includes a plan for market withdrawal at the end of the products life cycle. The life cycle management is strongly supported by risk management, partner management and corrective and preventative actions. Operating the risk management process makes sure that the risks associated with the use of the IVDMD are acceptable. Partner management includes controlling suppliers, delivery partners including software used in design, production and the QMS processes, and distribution partners. Corrective and preventative actions are implemented based on customer feedback or input from internal team to prioritise patient safety as the product is used. Sales and marketing operations from customer contacting to order handling and delivery operations are important for the operation of the company and its processes. All of the processes of

the company need to be maintained, improved, and reviewed. Quality system maintenance and improvement process ensures that the company processes and work instructions are up to date and improved to be compliant with relevant standards and the IVDR as well as the state of art of NGS practices. The quality system is annually reviewed in management reviews to ensure that improvements have been implemented and the QMS is compliant with regulations.

7.2 Implementing the quality system

Each document will be examined by three persons in the company, following the clause 4.2.4 of ISO 13485. As the first step, an author is identified based on their area of expertise that comports with the company process in question. The author can identify the required content to the document by examining the document content plan done based on the gap analysis. The author uses the QMS template document to ensure that the document contains relevant information to identify the document. After the author has written the document, it is reviewed by the reviewer who is familiar with the regulatory requirements considering the document. The reviewer can give notes to the author so that the regulatory requirements are met and the work instructions are clear and easy to follow. After the author has done possible corrections, the reviewer can sign the document and send it to the approver, who is the management representative. The approver approves the content of the document and can implement corrections if needed. After the approver has signed the document, it is considered as part of the company protocol and the content must be followed in daily work. If the process requires maintaining records of actions implemented according to the documents, those should be recorded and maintained. This process ensures that the regulations are followed and conformity to them is maintained.

Communication about following the new procedures established by the approved document must be implemented by the management. The compliance with following the procedures is evaluated in internal audits and management reviews

(International Organization for Standardization, 2016). External audits and certificates provided by authorities provide proven evidence of compliance. The certification of the QMS is out of the scope of this thesis.

7.3 Quality system documentation writing process

As Euformatics has been operating ten years, the company has established processes for product realisation. When developing the QMS, it is important to involve the people working with the process in writing the process description. Involving people outside the quality team helps to make the QMS processes coherent with the previous company operations and ensures that only necessary requirements are fulfilled. The quality system must not overload processes with extra work but to make sure that the process is executed similarly every time. For example, product realisation documentation was written in collaboration with the development team.

Time is also considered a valuable resource when developing the QMS. The transition periods of the MDR ending 26th of May 2021 and the IVDR 26th of May 2021 force economic operators to implement the QMS before the products can be released on the market. The pressure to be able to release products makes the QMS a high priority to any medical device or IVD company. That is why it is beneficial to have multiple people sharing the QMS writing process. As all documents need to be reviewed and approved, multiple people must overlook every process. If developing the QMS is a priority for all people in the company, the writing process will be smoother and fit the specific needs of the company.

Based on the gap analysis, a list of all documents needed for the QMS was made. An author, who has the responsibility of that the document will be written was assigned to each document. A reviewer was also assigned to all the documents. The writing process was combined with the Scrum process, where a ticket for each document was created and a certain number of documents were added to the weekly working process of the assigned authors. During the Scrum planning and review meetings, the

statistics of the writing process were reviewed and content or current problems with the documents were discussed. This process can also be expressed in terms of the PDCA cycle. Planning and the authors and implementing the schedule to Scrum is part of the *plan* step, writing documents is a part of *do* and reviewing and approving the documents is part of *check*. *Act* can be interpreted as producing the records defined in the written documents.

7.4 Applying the QMS requirements to each feature separately

In the software development process the features are developed and tested one by one. Therefore, it would be reasonable to apply the quality processes for each feature as it is going through the development process. The benefit of this method is that every feature is approved in advance before a product release and there will be no surprises or extra paperwork the day of the release.

This method of single feature approval was applied to the product realisation process. The product realisation plan describes the processes that are followed to transfer the idea of a product to a safe and functioning IVDMD on the market. The product realisation plan includes customer-related processes, the design and development process according to ISO 13485 and risk management process according to ISO 14971.

The design and development process begins with the design and development plan. The plan is the general description of the design and development steps that are performed to each feature or bug fix associated with the product release. First the plan describes where the inputs of design and development can come from. Inputs can come from customer feedback, through corrective and preventative actions, internal meetings or engineering change requests. The input is then documented as a Jira ticket, which is the design and development output. The ticket is then reviewed in an internal sprint meeting to approve the inclusion of that feature or fix into the next product release. The review result is documented to the ticket so that searching

for the reviewed tickets associated with a release provides a traceable list of features. The reviewed list can then be recorded to the design and development file. Verification and validation of tickets is implemented by status marking on the ticket. After the feature has been developed, the developer marks the ticked as resolved. After this, a tester validates and verifies the function of the feature and can mark the ticked as closed when the validation and verification of the feature are approved. After validation and verification, the feature can be approved to be transferred to the product to be released. The decision of transfer is documented to the ticket by the person responsible for the design and development process. The transfer marking is a searchable property of the ticket and a list of all tickets approved for transfer is recorded. Before a release, the development team hosts an internal meeting where the review and transfer records are checked and approved so that every step is performed according to the design and development plan.

Risk management can be performed alongside the design and development process when a risk management plug-in is used. There are multiple risk management plug-ins compatible with Atlassian tools. It is recommended to use a plug-in that can fulfil the requirements of ISO 14971 as this makes the process easier for single feature risk management. Similar to the design and development plan, a risk management plan describes how to implement risk management for each feature separately. The overall residual risk is determined after all risks associated with individual features are analysed.

8 Results

The results of the thesis consist of the results from the semi-structured interviews with six medical device companies and the action research on the development of a quality system. The software development process and the risk management process including the requirements of medical device standards and the IVDR are described.

8.1 Interview results

Six medical device companies operating in Finland where interviewed. The title of the interviewee, general description of the company's product and customer base are presented in Table 5.

Table 5. The companies interviewed.

Number	**Title of the interviewee**	**Products**	**Customers**
Company 1	Quality and Development Manager	Medical device software	Healthcare units
Company 2	Director of Quality systems and compliance affairs	IVD products, IVDMDs with embedded software	Healthcare units
Company 3	Director of Quality and compliance affairs	Medical device products, medical devices with embedded software	Healthcare units
Company 4	Senior quality and regulatory affairs manager	IVD products, IVDMDs with embedded software, supplier of IVD products	Healthcare units
Company 5	Quality Manager	Medical device software	Healthcare units
Company 6	Quality Manager	IVD products	Clinical laboratories

The interviewees were asked about ISO 13485 certification and the company's plans for the MDR/IVDR audit and certification. All of the companies interviewed had ISO 13485 certified QMS. Companies with pure software products were not in rush to certify their product under the MDR. The representative of company 5 stated that the company "has no huge pressure to certify under the MDR. Because no major changes are made to the product, it can stay on the market." This refers to the regulation on legacy products. Medical device and IVD companies with more products had made plans for the MDR or the IVDR audits in the near future, to be conducted during 2021 or early 2022. Half of the companies interviewed had already chosen a notified body, but one of these notified bodies was not qualified to audit the IVDR at the time of the interview. Company 2 had planned for the IVDR audit to take place in June of 2021. Company 3 had planned the MDR audit to take place in August or September of 2021. Company 4 found the situation of the IVDR notified bodies is challenging as there are currently only a few qualified notified bodies. At the time of the interview, company 4 had ongoing negotiations with notified bodies but had not chosen one yet.

One of the interview questions handled the topic of the risk class of the company's products and how it changes from the MDD to the MDR or respectively from the IVDD to the IVDR. Five of the six companies reported changes in risk classification. Both medical device software companies reported change from class I to class IIa under the MDR. All three IVD companies reported that previously all of their IVD products were self-certified. Under the IVDR these products will be divided into classes A, B and C. Additionally, one of the IVD companies will have products even in class D. Company 3 reported that the classification of products does not change from the MDD to the MDR. Two companies mentioned that some of their instruments and software used in combination with the instrument were separated into different risk classes.

The next questions addressed the standards and regulations that are important for the company and the quality system. The MDD and the MDR and respectively the

IVDD and the IVDR where mentioned by all companies as the most important regulation. ISO 13485 was important to all the companies. Risk management standard ISO 14971 was mentioned as important by four of the companies. IEC 62366 usability standard was mentioned by half of the interviewees, as was IEC 62304 software life cycle processes standard and ISO 15223 *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied*. MCDG guidance documents were highlighted as important by half of the companies. Additionally, specific regulations to an area or a country came up in some of the answers. Two of the companies are in the MDSAP program and FDA regulations were mentioned by half of the companies.

The interviewees were asked how their QMS was planned based on the MDR or the IVDR. Project schedule, resources and using consulting were also discussed. Four companies reported launching an official QMS project, and two companies reported that working towards MDR compliance was a gradual update rather than an official project. It was noted that the larger companies had official project and the two smaller companies did not. Those who reported a project had the same deadline as the IVDR or the MDR transition period end date. Company 3 started their QMS project with a five-day meeting in early 2019 where the goal was to schedule and budget the project and to divide tasks and responsibilities. The project was followed weekly, and the critical path was carefully inspected to keep up with the deadline. Two companies reported significant delay in their regulatory compliance project due to the COVID-19 pandemic. Company 3 had an original deadline of 26.5.2020 for their MDR project, but it was moved to 26.5.2021 as was the MDR transition period deadline. Company 3 representative commented: “COVID-19 pandemic slowed down the project, as it could not be progressed remotely.” The amount of people working on the QMS or regulatory compliance ranged from one person to around 20 people between the companies interviewed. Company 2 representative stated that the budget for their project was multiple millions of euros and around 20 people are working on the QMS fulltime. Consultation help used for the QMS was reported by five of the companies.

One of the interview questions was how the QMS documentation is arranged, managed, controlled and kept up to date. Half of the companies have a completely electronic documentation system, and the other half have a partly electronic documentation system and partly paper documentation. Electronic documentation systems that came up during the interviews were Atlassian Jira and Confluence, Q-pulse, M-files, and GitHub. Company 6 is transitioning towards a fully electronic document management system. Their documentation is currently manually signed. The quality team creates and updates documents and templates for the product development team to use. Their quality team is also responsible for reviewing the documents. Documentation updating schedule ranges from with every new software release to three-year cycles between the companies interviewed. Company 3 representative stated that ”the system takes care of the notification automatically and demands people to train themselves on process descriptions when either changes have been made or every two years.”

The interviewees were asked to describe what have been the most challenging areas of building the QMS. Fulfilling the requirements of technical documentation defined in the MDR or the IVDR was mentioned as a challenge by half of the companies. Post-market surveillance requirements were highlighted by two companies as were clinical evaluation or performance evaluation requirements. Company 5 highlighted the electrification of the QMS documentation as a challenge. “We would like the updating, approving and reviewing of documents to be more effortless and more automated. Especially during the COVID-19 pandemic, reviewing or updating process documents is difficult if it needs to be done in person”, told the representative of company 5. Companies 3 and 4 presented the regulations, processes and agreements relating to economic operators, that are new requirements under the MDR and the IVDR, as challenges for them. These companies have agreements with multiple importers and distributors which need to be documented into the processes and functions of the companies. One of the challenges of company 2 was the updating of labelling, packaging and instruction for use under the IVRD. The company has had to solve how to include the different

versions of labelling with different areal requirements on the global market. Company 6 was wondering if the bar they have set for their documentation is too high and takes too many resources. The company was wondering if some of the documentation could be made lighter.

ISO 13485 requires that the software used in the QMS and product realisation need to be validated before use**. The companies were asked how they validate these software tools.** Company 1 representative stated: "Software is validated so that they are appropriate for the intended use. First the need for validation is evaluated and then validation is done when needed. Validation includes determining the intended use of the software, determining the requirements and testing the software against the requirements, to see if they are appropriate for the intended use." Similarly, all companies reported a documented process for software validation. Risk based approach to validation was reported by four companies. Test cases for intended use were used by at least five of the companies.

One on the interview topics was about the kind of proof or study the companies use for clinical evaluation under the MDR or performance evaluation under the IVDR. Five companies reported scientific literature as the base of their clinical or performance evaluation. Company 1 representative stated that their clinical evaluation "will mainly be a literature study, because the software product does not have critical features for patient safety. We need to evaluate that the information that our software gives is accurate and clinically valid, mainly based on literature reviews." Globally there is a plenty of clinical information on the main feature of the software that company 1 intends to use in their study. Studies on their products in the laboratory or on the real user environment were performed by three of the companies. One company performed clinical evaluation by comparing patient results to those achieved with competitors' products.

The interviewees were asked what the company's approach to post-market surveillance is. Four out of the six companies answered this question. Company 2 follows the stability and development of their products. They look for sales numbers,

recalls, customer complaints, scientific publications related to similar products and publications of clinical evidence related to the products. Company 4 representative stated that they hold post-market surveillance meetings and a written report about each of their product every year.

One of the questions handled the type of the risk management system the company has. All companies had built their risk management process according to ISO 14971. Company 5 representative told that their risk management file includes risk management plans, analysis, reports, summaries, and benefit-risk analysis, as is required in ISO 14971. Before every product release in company 5, the need for updating the risk management file is assessed and the file is fully reviewed at least yearly. The MDR and the IVDR bring additional information security requirements to risk management. Company 4 representative talked about the nature of IVDMD related risks: "The IVD related risks are rarely related to patient directly because the patient or user is not physically in contact with the device that much. Risks are more related to interpreting results." The corrective and preventative actions process was mentioned as the method for handling process risks by half of the companies. Post-market surveillance was also mentioned as a part of risk management. **Additionally, the interviewees were asked if a risk management system could be built in Excel in their opinion.** Excel was mentioned as a possible tool by all companies, and it was used as the risk management tool by at least half of the companies interviewed. Difficulties in maintaining risks in Excel was mentioned by Company 3. Company 3 representative stated: "Using Excel is possible depending on the complexity of the product, but it is work intensive and somewhat risky… Traceability of requirements is work intensive in Excel… When one requirement changes, the whole document needs to be reviewed. With a risk management tool… risks can be managed as their own elements." One company stated that they were moving from Excel to Jira to manage risks. Two companies mentioned Jira as their risk management tool.

Medical devices and IVDMDs must have a unique device identification (UDI). **Does the company have a plan to implement UDI, or have they already implemented it?**

Five companies answered this question. The UDI implementation process was incomplete for all the companies. At the time of the interviews EUDAMED has not been completed and UDI implementation cannot be finalised. Four companies had chosen to use GS1, a company providing digital identifiers, as their UDI environment provider. Company 4 will implement UDI simultaneously when they are updating the product labelling. Company 6 will be using a labelling software that will print a QR-code-based UDI to products. It was noted by two companies that FDA requirements for UDI are different to the MDR/IVDR requirements.

The interviewees were asked what kind of results or experiences they have personally had from external audits. Five of the interviewees reported external audit experiences as positive, constructive, and co-operative. One of the interviewees felt like the notified body has purposely looked for something to mark as a non-conformity, but these non-conformities were small and easy to fix. Three of the interviewees mentioned that their company had gotten only minor non-conformities in external audits, the others did not disclose any results. Company 1 representative found the following aspects to be important before starting the external audit process: “Risk management is important for medical devices and technical documentation must be in order before starting the process. Documentation must be really good so that the notified body can evaluate it. With medical devices, the test results must be clear. The entire testing process must be clearly defined so that it can be determined is the testing done properly and is the product compliant with regulations and its intended use.”

What is the benefit to the company for building a QMS and complying with the MDR or the IVDR? All companies saw benefits with the QMS and following EU regulations. Company 2 representative said: “Following regulations is a prerequisite for entering the medical device market.” “A QMS is the only possible way to run a company this size… without a QMS everyone would do the work their own way.” Company 6 representative stated that complying with the IVDR is the most important goal for the company this year. Five companies mentioned safer or better-quality products

due to having a QMS. Company 2 representative commented: “When clinical evidence is proven, the doctor can assume that the result can be trusted. Respectively the patient wants the test result to be trustworthy and accurate.” Better competitiveness in tenders was mentioned by three companies. Company 2 representative said: “Often in tenders a QMS is required so that it can be ensured that the using the device does not endanger the population.”

Finally, the interviewees were asked if they had any additional words or anything to add about developing the QMS. Company 1 representative gave information on developing the QMS: “The development process should be started by looking at ISO 13485 requirements and starting to document how the requirement is accounted for in the company, e.g., how the company identifies documents in practice. Quality manual should be written according to the standard. A lot of conversations inside the company are needed, e.g. so that the Quality Manager does not write a purchasing process that will never be used. The Quality Manager informs others about the requirements and asks how the company accomplishes them and documents the process to the quality manual. After this, one should start looking at the MDR and what the regulation says about the same process. There are not many differences, but some additional requirements. The earlier a QMS is implemented the better. Situations and products change, and the more changes the more difficult to write processes and make them work if there are multiple ways company executes processes.” Company 2 representative reminded that every company must build a QMS that serves themselves. “The QMS is not stationary but a developing system that is developed based on company’s needs.” Company 3 representative emphasised that it is important to collaborate when developing the QMS. “It is always important to ask *what* and *why* before going into *how*. Good questions come from people who have not done a QMS before. Individual work is not good because that way there will be no commitment to the upcoming system and no reflection or challenging from the team.” Company 4 representative encouraged to remember that the reason the new regulations were written was patient safety. “The devices must work as intended and be safe and effective. It must be ensured throughout the

product life cycle." Company 4 representative also mentioned that one should not develop a too complicated QMS. The processes shall be compatible without contradictions. Company 5 representative wanted to emphasise automation of the documentation process. "Automation and making electronic reviewing possible should be invested into. Processes are difficult to change when there are a lot of manual steps. One should invest into a documentation management system that supports modern operating models… This should be minded by software companies where there is no factory where physical guide documents are needed." Company 6 representative encouraged the use of consultants: "There are IVD-experts that have long been in the field. If a company does not yet have a QMS, I would recommend using a consultant. Even if one had an understanding about requirements and how to develop a QMS, one could share viewpoints with a consultant."

8.2 Quality system processes

Even though Euformatics did not previously have a QMS implemented, gap analysis was identified as a useful tool to examine the areas lacking required documentation. Euformatics did have previous documentation on its processes, but these documents were found to require updating to comply with ISO 13485 and the IVDR. A part of the gap analysis is presented in Table 6.

Table 6. Example of the QMS gap analysis.

Topic	**Current state**	**IVDR/ISO 13485 requirement**	**Gap**
Design and development planning	Omnomics development process document, code review, CE matrix for testing	Plan and document design and development stages, including verification, validation, responsibilities and authorities, and traceability. Describe the plan to test the software. ISO 13485: clause 7.3	Updating the design and development documents to comply with ISO 13485 and updating the testing plan.

The QMS of Euformatics was built into Confluence, a team workspace provided by Atlassian. The structure of the QMS was based on the hypothetical structure presented in Figures 6 and 7. Confluence contains multiple spaces, and the QMS was mainly built to a companywide development (dev) space. The specific documents related to omnomicsNGS are located in the Confluence space named after the product. The dev space contains the company quality manual and SOPs, informing the employees on how the documentation process functions when creating Confluence documents or Jira tickets. SOPs, often containing charts are written about each process operated in the company. These SOPs are presented in Table 7.

Table 7. The SOPs of Euformatics.

Name of the SOP	**Description**
Euformatics processes	The document outlines all company processes using charts and figures.
Product realisation, production control	The document outlines product life cycle management, design and development process, product risk management, performance evaluation, post-market surveillance, traceability and identification, certification, market withdrawal and product support shutdown.
Purchasing, delivery partner and supplier selection process	The document outlines the purchasing process and how delivery partners and suppliers are chosen.
Management and human resources	The document describes the human resource processes, organisational structure and the responsibilities of the management.
Customer feedback and vigilance system	The document outlines how customer feedback is handled, reporting safety issues, implementing improvements, corrective and preventative actions and engineering change requests.

Name of the SOP	Description
Sales and marketing process	The document describes the sales and marketing operations of Euformatics.
Applicable standards and regulations	The document outlines which standards and regulations are followed by the company.
Guidance of personal data processing	The General Data Protection Regulation in the context of Euformatics' processes.

In addition to these SOPs, the Quality management system content document lists all the documents included in the QMS and shows the hierarchies of documentation by listing all the related documents under SOP titles. This hierarchy is made possible by adding labels into the documents. For example, all documents related to product realisation process are labelled *product-realisation*. This makes it easy for an employee to see which are the documents they need to follow while working on a certain process. The QMS content document also shows information about the document, as exemplified in Figure 9.

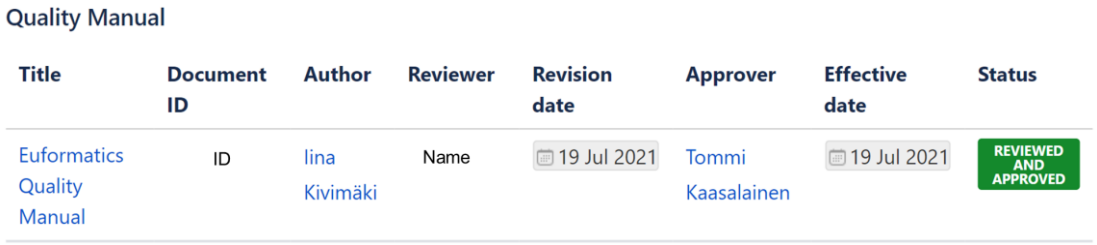

Figure 9. Example of the QMS content document.

The QMS content document automatically updates the information shown on the actual document. It shows the status of the document and when the document has been reviewed and approved. The employee can also access all the relevant documentation on this page. Sensitive information not intended to be accessible to all employees is stored in a separate cloud application with restricted access.

Work instructions, forms, records are accessible through the SOPs and the QMS content document. SOPs directly link to work instruction documents and forms

where applicable. Work instructions can be located as sub-pages of the SOP if located in the same Confluence space. Forms and records can often be found as sub-pages of the work instructions. Records also often exists in defined files, for example risk management file, design and development file and medical device file, that are linked to from SOPs and work instructions.

A QMS document template was created in Confluence to ensure that each document contains all the relevant information, and the status of all documents is visible to everyone on the QMS content document. The QMS document template is presented in Figure 10.

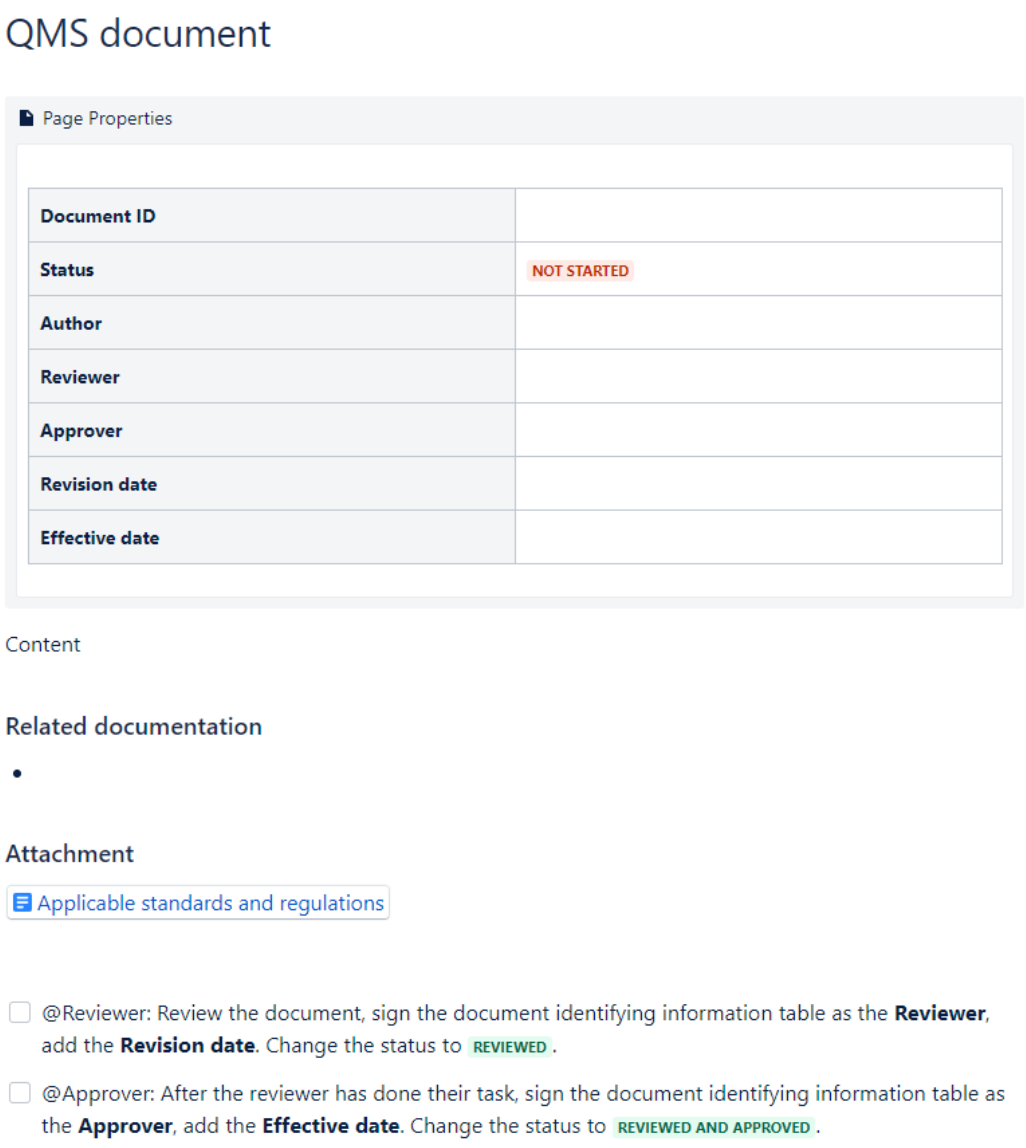

Figure 10. The QMS document template.

The QMS document template contains a table of information about the document. When the document is assigned to someone, they write their name, document ID, and change the status of the document to IN PROGRESS. The content is then written, and related documentation linked. Attachment shows the applicable standards and regulations that can be further specified in the document. Once the author is ready with the content, the status is changed to COMPLETE, and the reviewer and approver are assigned to the document by adding their names to the tasks at the bottom of the document. The system allows electronic signing of the documents. Once approved, the employees are trained to follow the document procedures starting from the effective date.

The design and development process of omnomicsNGS was written as described in chapter 7 as compatible with the Scrum development process. Figure 11 describes the process of including Jira tickets to the development process and which steps are needed for making a product release. The mandatory QMS documentation is produced by the system.

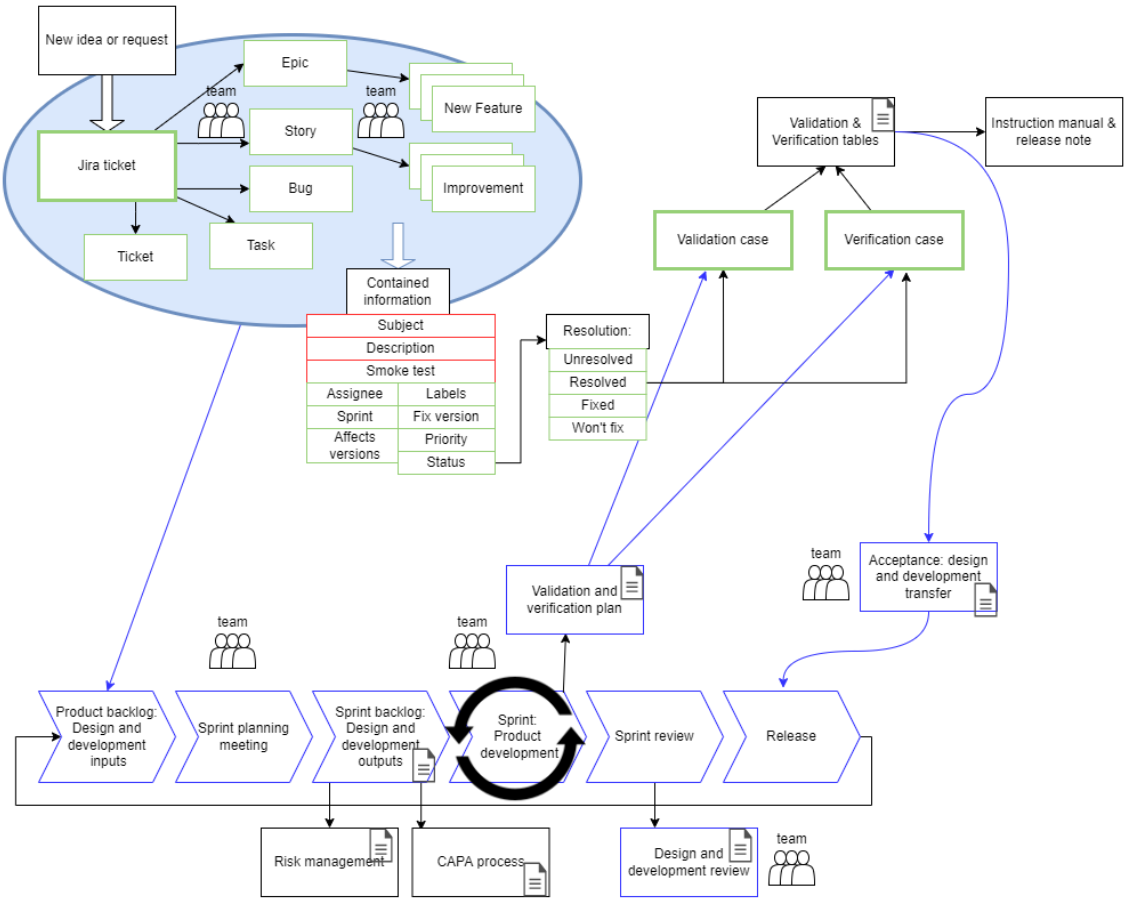

Figure 11. Description of the agile software development process modified to produce QMS documentation.

The process starts from the upper left corner, as a new idea for the product or a request from a customer is received. The request is formalised to the form of a Jira ticket. The type of the ticket is decided by the development team based on the content of the request. More vague requirements or entirely new functionalities can be written as *epics* or *stories* that are further formulated to *new feature* and *improvement* tickets. Bug fix tickers are typed as *bugs*, and other tasks or remarks are typed as *tasks* or *tickets*. All Jira tickets must contain *subject*, *description* of the requirement and details where the requirement comes from. The details of the requirements should be carefully described to ensure clear understanding and traceability of features. Additionally, tickets that are included to the design and development process must contain a *smoke test* that is a simple test that can be used by testers and certain customers to verify the feature. Tickets also include other

information, e.g. the person assigned to the ticket, a sprint in which the ticket is included, affected software version, fix version where the feature is included, labels, priority and status information.

All tickets in the omnomicsNGS project are included in the product backlog as design and development inputs. During sprint meetings it is decided which requirements will be developed and included into the product, forming the design and development outputs. These output tickets are labelled so that tickets can be called as a list of requirements in Confluence. The Confluence documents are indicated with a small document symbol in Figure 11. This design and development output document is then reviewed and recorded using the design and development review form during a review meeting. In this stage of the process, risk management and corrective actions are implemented. After the features, improvements or bug fixes have been implemented, the ticket is resolved and a verification and validation plan is made. For new features, two new tickets, one for validation case and one for verification case are made by the test engineer. Validation and verification plan is documented to Confluence, containing tables of all the validation and verification cases that need to be tested by the test engineer. Based on these features and testing, the user manual is updated, and a release note is written, containing the new features, improvements and bug fixes associated with the release. The testing of the features must be approved in a documented transfer meeting. Once the design and development outputs have been reviewed to meet product requirements and verified in the transfer meeting, a product release can be made.

Any bugs in the software that are critical, trending or reoccurring are implemented into CAPA process to find the root cause of the issue and solve the issue. In the internal audit it was noted that additionally to the normal development process, a process for hot fixes to manage and document emergency (customer specific) changes should be defined.

The validation and verification test tickets were sorted based on software pages on the product user interface. This makes the testers work more organised, as the tester

can open the Confluence page listing all the test cases that are associated with a certain software page, e.g. *Home*, *Workbench* etc. The Confluence page also shows and links the features that the test case is associated to, to ensure traceability of testing all features. Open test cases are listed on a separate list on the same Confluence page, ensuring that the tester notices all cases that have not yet been tested. The list shortens as the tester marks test tickets as closed. Positive comments from personnel involved with testing about the new organisation strategy of test cases were received after the implementation. In the internal audit of the QMS it was noted that a tester should also comment to the verification ticket that the case has been tested for the relevant release version. This ensures that the identity of the tester and the time of testing can be traced.

As Jira tickets were already used in the company before implementing the QMS, the product design and development process does not prolong the software release schedule. The requirements for the release are recorded to the Jira tickets and if the level of specificity of the ticket content is written as specified in the work instructions, the product development step does not affect the release schedule negatively. Similarly, validation and verification tickets already existed and the QMS requirements do not negatively affect testing as it is an important step of the product realisation process regardless. It should be assumed that the level of documentation in the development ticket content does not increase the amount of work for the software release, as understanding of features and bugs is crucial for the collaboration between developers and testers. However, the product release itself will require additional time as the team must arrange a meeting where it is inspected that all requirements for the release are done, and validation and verification are performed. Installation records, release note and updating the user manual will also take additional time. Figure 12 presents the presumed effect on the software development process in the context of the IVDR and medical device standards. The steps taking more time in the process compared to before implementing the QMS are highlighted with red colour, and the steps taking similar time than before the QMS implementation are highlighted with green.

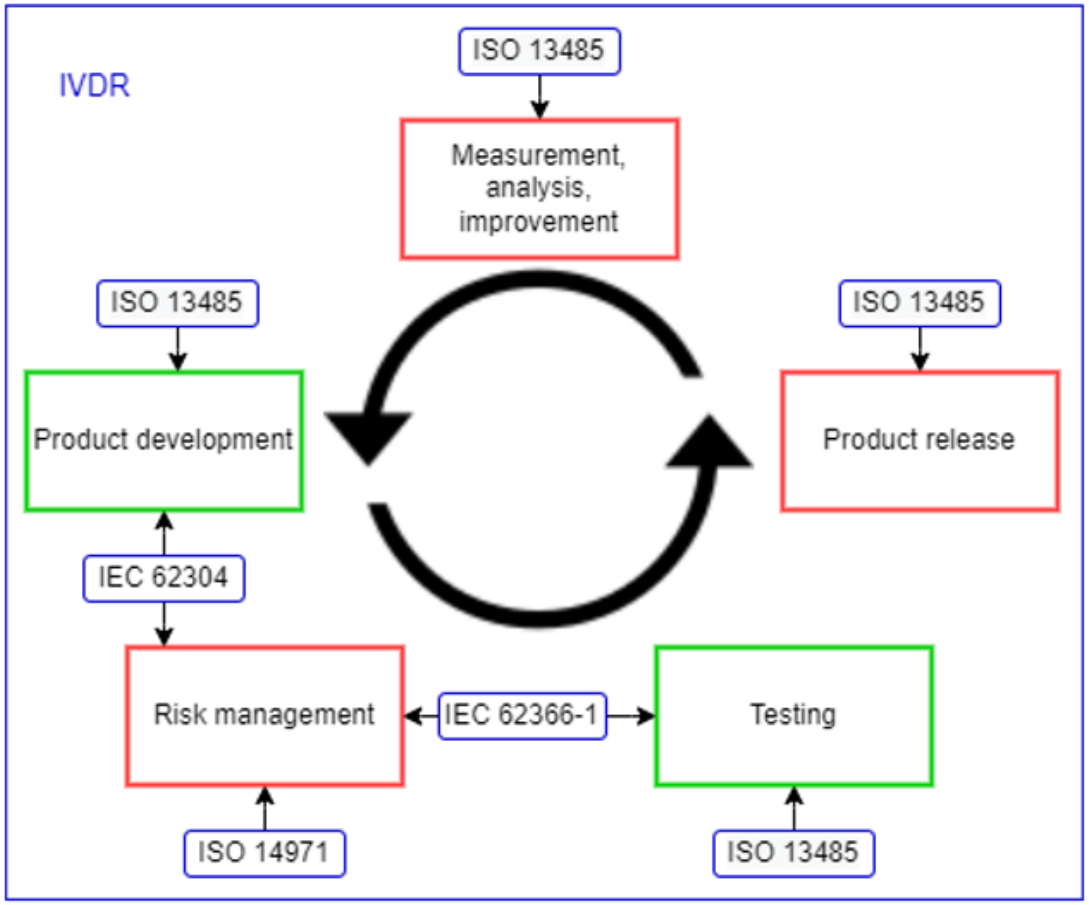

Figure 12. Critical steps in the software development process after implementing the QMS. The time-consuming steps are marked red.

In the internal audit it was noted that the requirements of IEC 62304 for software life cycle processes and IEC 62366-1 for medical device usability should also be considered in the development process. These requirements could increase the workload of the development process, especially depending on the safety classification of based on the IEC 62304. Software in safety classes B and C have additional requirements for documentation during the software life cycle.

Risk management tickets were implemented as separate risk tickets in contrast to adding risk analysis to the same ticket as the feature due to Jira functionalities. The decision was made based on the Jira plug-in chosen for risk management. There, additional text fields would have been needed to be added to existing tickets if risk management was written to the same ticket as the feature. This would make it

difficult to easily see all relevant information in the ticket. When the risk tickets are separate, a detailed risk analysis based on ISO 14971 can be written in the ticket description field. The ticket of the feature associated with the risk must be linked to the risk ticket to ensure traceability. In addition to product development related risks, input to risk management comes from software usability, corrective and preventative actions process, post-market surveillance and other QMS processes. Figure 13 presents an example of a risk ticket related to QMS training process.

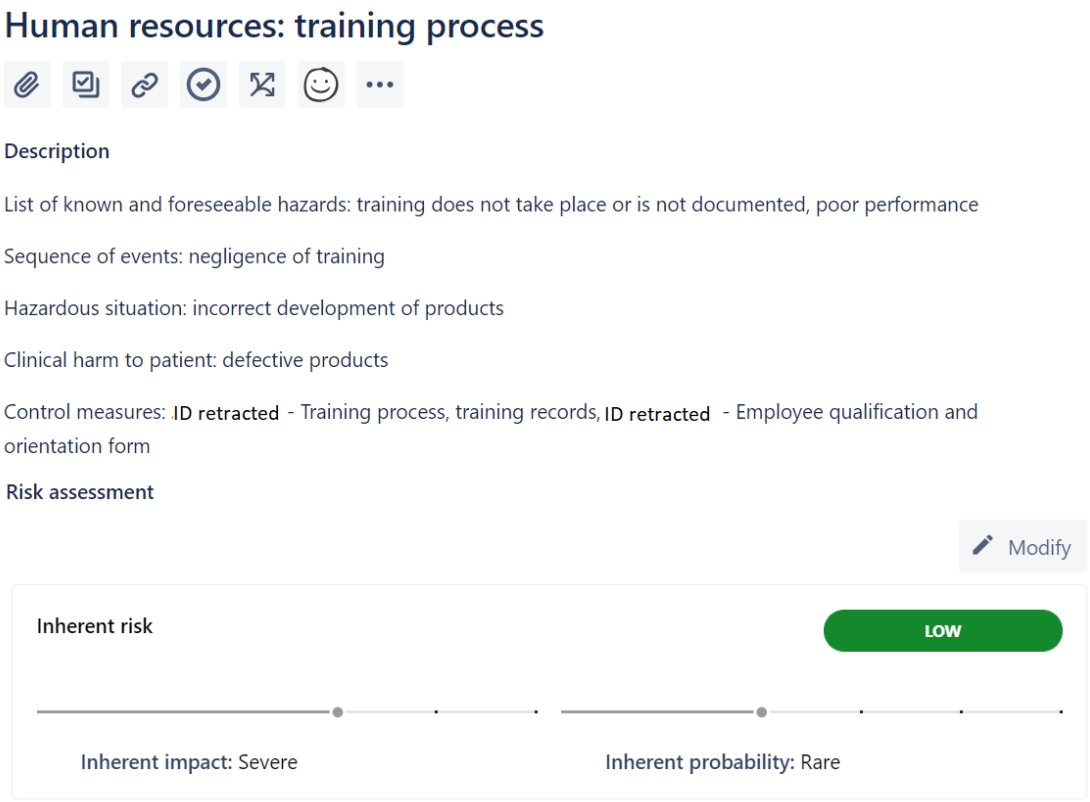

Figure 13. An example of a risk ticket related to QMS processes.

The description of the risk ticket contains all the risk analysis concepts presented in ISO 14971, including reasonably foreseeable misuses, characteristics related to safety, known and foreseeable hazards, sequence of events, hazardous situations and clinical harm to patient. Based on these concepts, the probability of harm and the severity are determined on a scale of 1 to 5. The scale can be seen in the risk matrix in Figure 14. The risk plug-in automatically uses probability and impact as the risk assessment concepts. The connection of severity and impact is explained in risk

management SOP to make the plug-in compatible with the risk management process. Possible risk control measures are linked to in the ticket. In this example, the control measures are QMS documents and records. After implementing control measures, residual risk assessment is then performed similarly as inherent risk analysis.

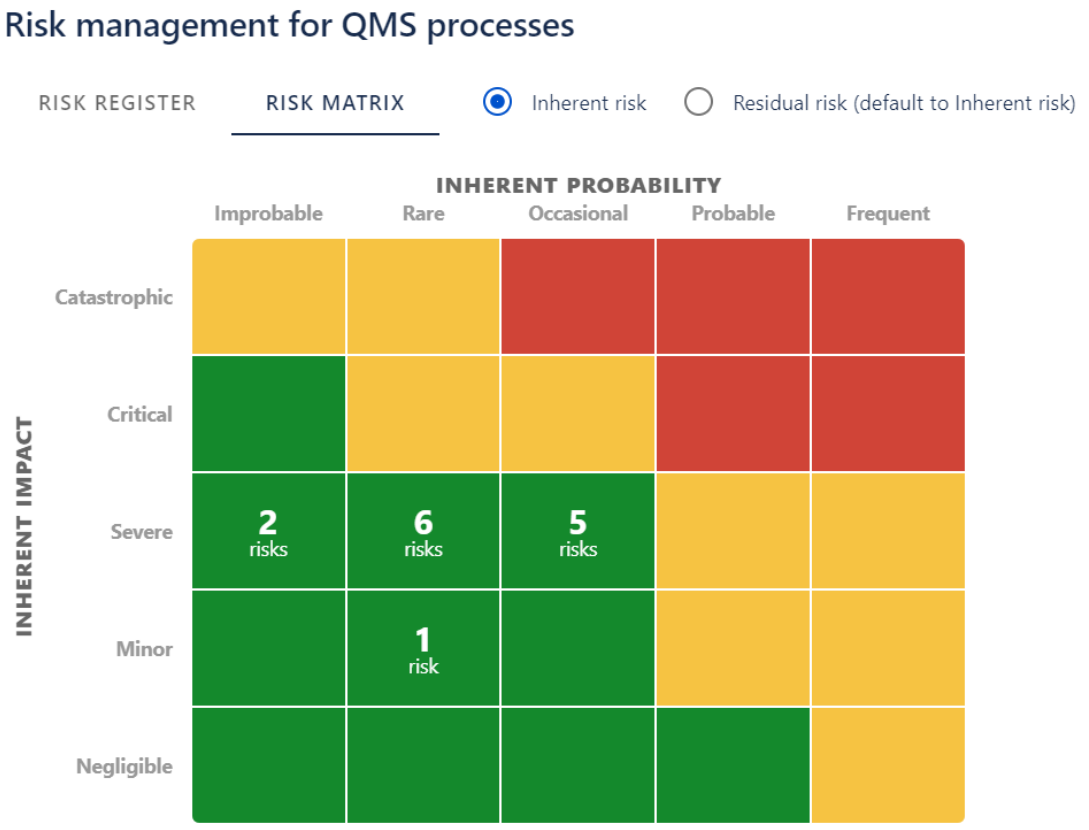

Figure 14. An example of a risk matrix of the QMS risks.

The acceptability of the risks is easily seen in the risk matrix. The acceptable risks are indicated with green colour. Medium risks are indicated with yellow colour. Medium risks are acceptable if control measures have been implemented and risk is reduced as low as possible, and the benefits have been judged to overweigh the risks. High risks are indicated with red colour. High risks are unacceptable and need to be mitigated with control measures. The overall residual risk is acceptable, when all separate residual risks are acceptable or can be approved based on the benefit-risk analysis and the benefits related to the product outweigh the overall residual risk. Risk management is reviewed and recorded in review meetings before major product releases. Risk management will introduce an additional step to the software release

process once the QMS is implemented. Particularly in the beginning phases of implementing risk management and training personnel to create risk tickets is time-consuming. Risk management is highlighted as red in Figure 12 as it can slow down the software release schedule.

When validating software used in the QMS and product realisation according to ISO 13485, the company needs to implement a risk-based process as demonstrated by the interview results. A risk-based process for software validation was also implemented in Euformatics, where software features were compared to the requirements of the company and standards. Based on the risk level, test cases were implemented to prove that the software could be used to build a safe product or QMS. When appropriate, the risks related to the use of the software were written as tickets, assessed and control measures for mitigating the risk were written. In case of Euformatics, software used in the QMS and product realisation includes Confluence, Jira and risk management plug-in, as well as other software used in product realisation. In an internal audit it was noted that the usability requirements the company has for the software should be more prioritised in the validation process. The validation could be built based on use cases of the software.

Performance evaluation of omnomicsNGS will likely be conducted based on scientific literature review and validation and verification testing of the product features. A plan for demonstrating scientific validity and analytical and clinical performance is documented to the performance evaluation plan and the results will be presented in the performance evaluation report. The evaluation will be updated throughout the products life cycle. Similarly, a plan for post-market surveillance will be implemented, containing areas that surfaced during the interviews: sales numbers, customer complaints, scientific publications related to similar products and publications of clinical evidence related to the products. The implementation of the UDI will be documented as a part of the traceability and identification process. Most likely GS1 will be used as the UDI issuing entity as did the companies interviewed. Additionally, processes for improvement (CAPA), data analysis and monitoring and measurement

of products and processes are implemented. These processes will increase the amount of documentation needed and can slow down the software release schedule, as reflected in Figure 12. However, these processes should be considered as useful in improving the product and making sure that compliance to regulatory requirements is achieved. Jira is utilised in the CAPA process and feedback collection and complaint handling as much as possible to ensure traceability and easy access to relevant records.

9 Discussion

Certifying ISO 13485 QMS is perceived as beneficial, as demonstrated by all the companies interviewed even though certification is not mandatory. The benefits are perceived to aid in tendering processes and improve the quality of the products. Due to the benefits, Euformatics' decision to first start developing the QMS according to ISO 13485 is sensible. This approach was supported by company 1, which is also a software developing company. Once the QMS and technical documentation are finalised, the manufacturer needs to start negotiations with notified bodies, as the CE certification process can take a long time. Form the interview results one could assume that companies with software products are not in a rush to certify their products according to the MDR as class I devices can be sold as legacy products until 2024 (European Parliament & Council of the European Union, 2017a). However, not aiming to comply with the regulation severely limits the possibilities to product development as major changes are not allowed in legacy products. Based on this fact it is beneficial for any manufacturer of medical devices or IVDMDs to aim to be regulatory compliant as soon as possible.

According to research conducted by Bujok et al. (2017) it is common to encounter software companies in the health technology that have expert knowledge on software development but little knowledge on how to apply regulatory requirements and standards. As the documentation increases, small companies have difficulty in allocating resources to maintain the documentation required by regulations. (Bujok et al., 2017) This was also noticed in the scope of this thesis. The company had allocated some resources to consulting services to familiarise with the IVRD, action on the implementation of the QMS could be taken only after hiring personnel for the project. Finding a competent person to be the person responsible for regulatory compliance may be a challenge for some economic operators when looking to become compliant with the regulation. The position is challenging as the

responsibility is substantial. The regulations are new to economic operators and the interpretation of rules is not yet established.

The MDCG provides guidance documents to follow the medical device and IVD regulations (European Commission, 2021b). However, even in 2021, the number of guidance documents specific to the IVDR is minimal. There are ongoing documents that the MDCG is working on but as the transition period of the IVDR is ending in May 2022 and if extension to the timeline is not granted, the guidance comes a little too late to operators who need to make the transition. Still, the upcoming guidance will be beneficial for new economic operators willing to participate on the IVD market. Added guidance and communication about the regulation would increase the customer understanding of the IVDR.

Research conducted by Bujok et al. (2017) found that the guidance on medical device classification was lacking. There is a need for public record of devices and regulations, so that manufacturers can compare their risk classes and similar devices would end up in the same class. The problem was also identified in this thesis when classifying omnomicsNGS. The study conducted by Cobbaert et al. (2021) found that for some manufacturers, the classification of devices can take multiple rounds of communication with the notified body.

The change in classification rules from directives to regulations is a large challenge especially for IVDMDs as most devices cannot be self-certified anymore. Medical software classification is also changing and keeping devices in low risk classes would be difficult to rationalise in terms of the new rules. Economic operator must be careful with the classification rules. MDCG guidance documents on the classification rules could aid the decision process. It could be helpful to use a consultant to help establish the risk class and intended use. This thesis cannot provide the answer on how to classify NGS variant interpretation software due to the difficulty in rule interpretation. It would seem to be the safest option is to use the IVDR classification rule 3 (i) in Annex VIII: “Devices are classified as class C if they are intended for human genetic testing” (European Parliament & Council of the European Union, 2017b).

Class B could be also considered as the IVDR doesn't specify which devices are in class B and this would be in line with the MDR common software classification IIa. Implementation rule 1.4 of Annex VIII of the IVDR states that if the software drives or influences the use of a device, the software is classified as the same class as that device. If the software is independent of any other device, the software is classified based on its own intended use. MDCG guidance 2019-11 interprets that is the software is needed to render raw data to a readable form for the user, the software is considered to drive or influence the IVDMD (Medical Device Coordination Group, 2019). For any similar devices, using consultant help is highly advised.

When planning the development and implementation of the QMS, it depends on the company size and targets if an official project is needed to be launched. From the interviews it was concluded that larger companies had a QMS project and smaller companies made gradual changes to their systems. The regulatory/quality management team size is also depended on the size and number of products of the company. Multiple working solutions are possible when developing a QMS, and the best way is specific to that one company. Consultations are valuable help for many companies and is recommended to be used in the QMS development process. In Euformatics, the QMS project started with familiarisation to the regulation and performing gap analysis. Project approach and scheduling was important in the company to ensure that the QMS would be implemented in the timeframe set by the management.

As noticed from the interview results, there is a shift from paper QMSs to electronic systems. Both are still used and valid for building the QMS. Multiple different platforms can be used for documentation. As Confluence and Jira were in use at Euformatics before the QMS implementation was started, they were a natural choice for the company. It is good to have automatic systems that remind the users when documents need updates, but this can be done manually also. Frequently updating documents is clearly important in building a trustworthy QMS based on interview answers.

The IVDR and the MDR have brought new requirements that increase the amount of documentation a QMS is required to produce. In addition to regulatory challenges, the interviewees brought up general documentation challenges like automation and knowing the minimum required level of documentation. In the case of Euformatics, the current level of documentation is based on the internal judgement of the company. The final level of documentation required is defined by the notified body. MDCG guidance documents, consulting and outsourcing internal audits provide help in these problems.

For conducting performance evaluation (or clinical evaluation) it can be concluded based on the interview results, that if the medical device products do not cause critical damage to patient's health or there is plenty of research and data on the area of study, basing the evaluation on scientific literature may be enough for demonstrating clinical or performance evaluation. Conducting a performance or a clinical study may not be necessary if the economic operator can use other methods to demonstrate clinical performance. Another common way to demonstrate clinical and analytical performance can be to perform testing in a third-party laboratory. Post-market surveillance is one of the other requirements of the MDR and the IVDR. From the interview results it can be concluded that by collecting data on the company's product and performance, adjustments can be made to increase the safety, effectiveness, and usability of the product. Post-market surveillance also provides information on the competitiveness of the product compared to other similar products on the market.

As corrective and preventative actions and post-market surveillance are requirements for the QMS set by ISO 13485 and the MDR or the IVDR it can be assumed that all companies will use these processes as part of risk management once the process descriptions are completed, accepted, and implemented. Based on the interviews, Excel is still widely used in risk management, though other options like Jira plug-ins are available. The best option for the company depends on the type and number of products. It also depends on the simplicity of the product, as small number

of low risks can be more easily maintained in Excel. The risks associated with IVD products may be difficult to determine, as the patient may not be in direct contact with the device. As stated in chapter 8.1, the IVD device risks are often related to the interpretation of patients' test results. An IVD manufacturer should carefully consider what are the risks associated with the result interpretation process and what could be the severity and probability of harm to the patient if the risk is actualised.

The documentation and traceability challenges presented by Heeager & Nielsen (2018) and Kostić (2017) where addressed in this thesis by implementing QMS documentation requirements into the software development process. The QMS documentation process cannot often be described as light, but with careful planning of the process, documentation and traceability requirements could be combined with agile methods. Traceability of features and testing is ensured by linking related tickets to each other. Agile process still allows involving users and customers in the development process as recommended by Py et al. (2021). Sprint meetings are an important place to plan the releases and the features included in them as supported by Heeager & Nielsen (2018). The development process presented in chapter 8.2 also allows detailed planning of testing, which was another concern presented by Heeager & Nielsen (2018), by creating validation and verification tickets for all features.

The separation of risk tickets and feature tickets is both supported and opposed to by the literature review. The abuser stories suggested by Heeager & Nielsen (2018) could be interpreted as the risk tickets separated from the product requirement user stories. Even though the research of Stirbu & Mikkonen (2018) suggested that the separation of risk management process freezes the development process, the traceability of linking features and risk tickets enables separating these processes as presented in chapter 8.2.

It is clear based on the interview answers that when the processes are well planned and documented, the external audit of the QMS will be a positive experience. External audits should be used as learning experiences to further develop processes. Minor non-conformities are common and should be perceived as positive learning

opportunity. Audits help the development process to produce a tool that can be trusted by the user. As many manufactures do not have earlier experience on notified body audits, problems to comply with the regulations can occur. These problems can result in delays releasing products onto the market. Internal audits performed by experienced consultants will be helpful in understanding the requirements of compliancy.

Following regulations is a prerequisite for entering the medical device market and proving the safety of the products. The QMS is different for each company. Collaboration and discussion between different processes inside the company is important for a functioning QMS. For a software company increasing the automating of processes is important to be able to comply with the minimum regulatory requirements.

Current problems the IVD regulatory field are related to the limited number of approved notified bodies and the 2022 deadline. EUDAMED is not fully functional, and this affects QMS processes as the final processes cannot be defined for example for UDI implementation. According to Cobbaert et al. (2021), the certification process of class B and C devices will take up to 13 months and the infrastructure and expert laboratories needed for class D certification are lacking. Companies aspiring to comply with the IVDR are left questioning if the time and resources enable the conformity to IVDR withing the transition period. This problem of not complying to IVDR early enough will likely to be realised for many economic operators on 26th of May 2022 if immediate action is not taken by the economic operators themselves, as well as the European authorities making possible accommodations. The new regulation will lead to discontinuation of some products manufactured under the IVDD and limit the amount of diagnostic or treatments solutions for patients (Cobbaert et al., 2021). A proposal for extending the transition period from the IVDD to the IVDR has been issued. The proposal highlights that 95% of the IVD devices that would require a notified body certificate do not yet have one. Longer transition period would relieve this difficult circumstance. (European Commission, 2021c)

It is unclear how the IVDR will affect when selling IVD products outside of Europe. Economic operators will have to allocate resources to complying with multiple regulations on the global market. It would be beneficial to develop global regulations resembling MDSAP based on the medical device standards which would be recognised globally.

10 Conclusions

This Chapter answers the research questions introduced in the first chapter. Recommendations for future work are also given.

What are the minimum requirements for implementing a quality system that is not too laborious for a manufacturer to maintain and is simultaneously beneficial in terms of patient safety?

Based on the literature research, interview results and the quality system process results presented in chapter 8.2, the requirements for implementing a QMS for a software development process were defined. The approach chosen was to develop the QMS according to ISO 13485 and then add the additional requirements of the IVRD. The requirement of other harmonised standards should also be considered. As there is not a single way to conform to the QMS requirements, the minimum requirements for the QMS are dependent on the individual company, the number of products and their risk classification. Even though the initial guess on the minimum requirements is done by the manufacturer based on these factors, the extent of the content of QMS documents is finally determined by the notified body.

Implementing a QMS fulfilling the regulatory requirements will inevitably increase the amount of work needed in the software release cycle, as demonstrated in Figure 12. The impact of the QMS requirements to the length of the software development cycle could be further studied by monitoring the working hours used for each step in the cycle.

What kind of software development method can be used in the medical device framework?

The agile nature of software development must be modified to more traditional approach even with complying with the minimum requirements of medical device manufacturing. The key elements of product development and testing can remain in

the style of agile process but ensuring that enough resources is allocated to documenting improvements, non-conformances, monitoring and release records. Implementing these QMS processes is worth the effort as they are the prerequisite for IVD manufacturer to keep their products on the market.

How does the development process produce a tool that can be trusted by the user?

Following the development process described in chapter 8.2 is likely to produce a tool that can be trusted by the user. The product must support the traceability of features to ensure patient safety. The implementation of the UDI will ensure that the product can be traced if harm to a patient has occurred. The demonstration that the product functions according to the regulations is done by validation and verification testing described in the development process. Additionally, the instructions for use are updated and release notes are written with every release to ensure that the user is aware of all features and functions.

How can the quality system ensure that the product is able to compete on the market and does not lower the usability of the product?

The quality system must be able to demonstrate that the manufacturer of a medical software operates according to the regulations. Based on the quality system process results, there was no evidence that the usability of the product would be decreased by the QMS process compatible with ISO 13485 and ISO 14971 requirements. The software development process is receptive to changes and customer requests, while producing records of the product requirements, implementation and testing. The QMS has a process for improving the company processes and product and that way the usability can also be improved. In the future the product will likely be IVDR compliant, continuing to support NGS tertiary analysis. The ability to comply with QMS standards indicates that regularity compliance is possible with modified agile software development processes. Implementing IEC 62366-1 standard on usability engineering is likely to further increase the usability of the product. When future work is done to develop the QMS, Euformatics can certify ISO 13845 quality system,

and finally CE mark under the IVDR. The impact of these actions to the competitiveness on the market is likely to be positive, considering that the compliance with the regulations is mandatory. Economic operators not willing to comply with the regulations will be dropped from the market.

How can the quality system be set in place without hindering the tool from swiftly evolving together with the field of molecular genetics?

The modified agile software development process enables swift evolvement of the genetic tool. However, the strict requirements of the IVDR may hinder significant changes due to the lengthy conformity assessment by notified bodies. In the future it will be important to study the balance of evolving technologies, developing new innovations and the regulation of these technologies.

How are other medical device companies developing their QMS to comply with the IVDR or the MDR.

Certifying ISO 13485 QMS is perceived as beneficial, as demonstrated by all the companies interviewed. In addition to ISO 13485, other common medical device standards were brought up by the interviewees. The more these standards are applied to company processes, the more the QMS and company processes can be improved. The standards used depend on the type of the company's products, e.g. software life cycle standard IEC 62304 would be commonly used by software companies. By following these standards, companies and their customers can be confident that the company is able to produce a tool that can be trusted by the user. Certificates of following the standards are also ways to compete on the market.

The compliance with the MDR or the IVDR is a new challenge to all medical device companies. All companies must make an initial guess of compliance individual to the company's products and size. After this, the improvements of the QMS should be continued throughout the company life cycle. The main motivation to produce medical devices should always be the safety of patients and the high effectiveness of the devices.

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Guiding questions for the interviews

APPENDIX 1

1. Describe the product and customers of the company.
2. What are the plans of the company regarding ISO 13485 certification and the MDR/IVDR auditing?
3. Does the risk class of the company's products change from MDD to MDR or respectively from IVDD to IVDR?
4. Which standards and regulations are important for the company and the quality system?
5. How was the quality management system planned based on the MDR or the IVDR? Project schedule, resources and using consulting were also discussed.
6. How is the QMS documentation arranged, managed, controlled and kept up to date?
7. What were the most challenging areas of building the QMS regarding ISO 13485 or the MDR/IVDR?
8. ISO 13485 requires that the software used in the QMS and product realisation need to be validated before use. How does the company validate their software tools?
9. What kind of proof or study is used for clinical evaluation (MDR) or performance evaluation (IVDR)?
10. What is the company's approach to post-market surveillance?
11. What kind of risk management system the company has? Can you build a risk management system in Excel?
12. What kind of results or experiences the Quality Manager has from external audits?
13. Devices must have unique device identification. Does the company have a plan to implement UDI, or have they already implemented it?
14. What is the benefit to the company for building a QMS and complying with the MDR/IVDR?
15. Any additional words or anything to add about developing the QMS?