USE OF DIGITAL TECHNOLOGIES IN HEALTHCARE: APPROVALS IN THE BORDERLINE AREA BETWEEN MEDICAL DEVICE AND MEDICAL AID – INVESTIGATION AND EVALUATION OF REGULATORY CHANGES AND CHALLENGES - MEDICAL SOFTWARE APPLICATIONS

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AIMD	Active Implantable Medical Device
AIMDD	Active Implantable Medical Device Directive
AMD	Amendment
App	Short form for "Application"
BfArM	German Federal Institute for Drugs and Medical Devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte)
BMG	German Federal Ministry of Health (German: Bundesministerium für Gesundheit)
BWP	Biologics Working Party
CE	Communauté Européenne
CHMP	Committee for Human Medicinal Products
CSV	Consolidated Version
DiGA	Digital Health Application (German: Digitale Gesundheitsanwendung)
DiGAV	Digital Health Applications Regulation (German: Digitale-Gesundheitsanwendungen-Verordnung)
DVG	Digital Health Care Act (German: Digitale-Versorgungs-Gesetz)
DVPMG	Digital Care and Nursing Modernization Act (German: Digitale-Versorgung-und-Pflege-Modernisierungs-Gesetz)
EC	European Commission
EEC	European Economic Community
eHealth	Electronic Health
EHR	Electronic Health Record
EMA	European Medicines Agency
EMR	Electronic Medical Record
en	English
EU	European Union

Abbreviation	Explanation
Eudamed	European database on medical devices
GSAV	Law for more safety in the supply of medicines (German: Gesetz für mehr Sicherheit in der Arzneimittelversorgung)
ICT	Information and Communication Technologies
IEC	International Electrotechnical Commission
ISI	Fraunhofer Institute for Systems and Innovation Research
ISO	International Organization for Standardization
IVDD	In Vitro Diagnostic Directive
IVDR	In Vitro Diagnostic Regulation
MDCG	Medical Device Co-ordination Group
MDD	Medical Devices Directive
MDR	Medical Devices Regulation
MEDDEV	Medical Devices (Guideline(s))
mHealth	Mobile Health
MPAMIV	Medical Devices User Notification and Information Regulation (German: Medizinprodukte-Anwendermelde- und Informationsverordnung)
MPBetreibV	Medical Device Operator Regulation (German: Medizinprodukte-Betreiberverordnung)
MPDG	Medical Device Law Implementing Act (German: Medizinprodukterecht-Durchführungsgesetz)
MPEUAnpG	Medical Device EU Adaptation Act (German:Medizinprodukte-EU-Anpassungsgesetz)
MPEUAnpV	Medical Device EU Adaptation Regulation (German: Medizinprodukte-EU-Anpassungsverordnung)
MPG	Medical Devices Act (German: Medizinproduktegesetz)
ONC	Office of the National Coordinator for Health Information Technology

Abbreviation	Explanation
	(US)
PC	Personal Computer
PDSG	Patient Data Privacy Act (German: Patientendaten-Schutz-Gesetz)
PEI	Paul-Ehrlich Institute. Federal Institute for Vaccines and Biomedical Drugs (German: Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel)
PMS	Post-market surveillance
PSUR	Periodic Safety Update Report
QM	Quality Management
QWP	Joint CHMP/CVMP Quality Working Party
SGB	German Social Code (German: Sozialgesetzbuch)
SOP	Standard Operating Procedure
TI	Telematic Infrastructure
TSVG	Appointment Service and Care Act (German: Terminservice- und Versorgungsgesetz)
UDI	Unique Device Identification
UDI-DI	Unique Device Identification-Device Identifier
WHO	World Health Organisation
ZLG	Central Office of the Federal States for Health Protection with regard to Medicinal Products and Medical Devices (German: Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten)

1 INTRODUCTION

1.1 Background

Digitalization is one of the buzzwords that has become indispensable in recent decades. Due to the constant progress in the technological field, applications are possible today that might have been considered music of the future or science fiction just a few years ago. The progress of digitalization and its acceptance in society becomes clear if we take as a basis the development of Internet use within the population. For example, Internet use among the German population was just 37% in 2001; by 2021, this had already grown to 91%. And mobile Internet use also increased from 54% to 82% in the period from 2015 to 2021. [1]

However, digitalization has not stopped at the medical sector either. The term "digitalization in the healthcare sector" describes as an overarching term what can be associated in the widest sense with the use of electronics in medicine and the care of patients. Various areas of application are included under this term. These are primarily eHealth (use of electronic devices in the healthcare sector), mHealth (use of mobile eHealth applications), telemedicine (medical services provided digitally by healthcare professionals) and the Telematics Infrastructure (TI), which covers the networking and interoperability of the individual components and applications within eHealth. [2] It is thus evident, that the digital transformation in the medical sector brings opportunities and possibilities to revolutionize and improve the medical landscape through the use of the above mentioned “e-Health technologies and tools”. According to the WHO definition, eHealth is meant to be “*the cost-effective and secure use of information and communication technologies (ICT) in support of health and health-related fields*” [3], which covers the whole range of possible applications.

Digitalization in the medical sector has a long history. What began with the introduction of the first imaging techniques at the beginning of the 1970s, continued to evolve over time. [4] Methods were improved and refined, and new ones were added. The range of applications of digital technology was constantly expanded, and what was initially reserved for medical professionals was then also available to a certain extent to private users or patients by use of electronic devices such as computers, tablets and smartphones and correspondingly adapted applications (apps) as stand alone applications or in combination with medical devices.

According to the forecast of the online data platform and statistics database statista.com, sales in the eHealth segment will amount to around 57.30 billion € worldwide in 2022 and increase by 10.26% to circa 93.38 billion € by 2027. [5] This gives an idea of how large the emerging market will be in the next few years. The variety of digitally deployed technology in the healthcare sector is immense and today it is impossible to imagine life without it (see Section 2). However, the exponential growth of the digital industry, with its wide range of applications and possibilities for use, has not only positive effects. The medical sector is one of the most highly regulated within our society, as safety aspects of the use on humans and especially with regard to vulnerable patients must always be considered with the highest priority. Due to the variety of possible applications, both manufacturers and authorities are increasingly confronted with the question of how the placement of these diverse technologies on the market and their further maintenance should be managed in order to guarantee the greatest possible security of the products, both from the technical point of view and also from the data protection perspective.

As a result, the so-called "Digital transformation“ plays a significant role in the advancement of the medical sector. Therefore, it is supported and accompanied by governments worldwide. This is reflected in numerous comprehensive legal frameworks designed to ensure the safe marketing and use of the digital components (see also Section 3).

Despite all efforts to drive digitalization forward more vigorously, a 2018 study by the Bertelsmann Stiftung shows, that Germany is one of the countries at the bottom of the ranking (rank 16 out of 17 countries surveyed) when it comes to determining the status of digitalization of the national health system of Germany in an international comparison with other countries. [6] This is also noted by McKinsey & Company, one of the world's leading management consulting firms, in its annual *eHealth Report* on the status of digitalization progress in Germany. Although a progress in use and creation of framework conditions can be observed, and despite of Germany being the precursor in approval and reimbursement of digital health applications, the benchmarking shows that Germany still cannot keep up in an international comparison. [7] A recent study by the Fraunhofer Institute for Systems and Innovation Research (ISI) in 2022 shows that up to now digitalization in Germany is still progressing only very slowly and still ranks at the lower end of the scale in an international comparison. [8]

Most countries have already established a clear lead. In order not to lose touch with the European healthcare system as a whole, the German government has increased its efforts in the area of digital technologies and launched initiatives to drive forward the transformation in the healthcare system more strongly and to better exploit the potential for digitalization. The summary of the Bertelsmann study report once again emphasizes that "*Digital solutions can improve patient safety, enhance the quality of treatment outcomes and increase the economic efficiency and sustainability of a healthcare system.[Translated from German]*" [6]. Numerous established companies and start-ups, especially in the medical device and software sectors, have recognized the enormous potential and are driving digitalization forward with an increasing number of innovative developments.

However, the use of new digital technologies has not only advantages but, as already mentioned, a lot of risks that must be taken into consideration, too. Since, for example, an increasing number of electronic applications, such as apps, are now also being used to support decision-making in the medical field of diagnostics and treatment of patients,

safe use and the guarantee of harm-free use or avoidance of damage for the patient, especially in the event of any malfunctions or failure of the technical devices, obviously play a decisive role. And once again the manufacturers and the regulatory area are confronted with problems and challenges, since eHealth technologies are to a great extent innovations for which there are nearly no traditional procedures to fall back on for approval and maintenance.

The development of software for the medical or pharmaceutical sector is a tremendous task for both the developers and manufacturers of devices, respectively, and also the approving bodies, which requires detailed planning in advance. The rules and regulations for medical devices (see Section 3) are constantly being updated and supplemented, and have to be monitored, so that many aspects have to be taken into account, which should ultimately contribute to the software being able to be brought to market in a way that is useful for its intended purpose, and easy and error-free for users to operate. As with the placing on market of medical devices in the conventional sense (see Section 4.2), the safety aspects to be taken into account are of decisive importance. But not every software for the medical field can necessarily be declared as a medical device and approved as such. How software is ultimately qualified and must ultimately be subjected to regulatory processes depends largely on its intended purpose within the scope of use (Section 4.3). The manufacturers and also the regulatory area are confronted here with a major hurdle in the form of comprehensive legislation (Table 1, Table 2), which certainly does not yet cover and cannot cover all open points and questions of this still quite young and dynamic branch of the medical device area.

As digitalization will play an increasingly important role in all areas of life in the future, especially in the medical device area, it is essential to take a closer look at the topic of software development and application in this context, specifically taking into account the influence of the Medical Device Regulation (EU) 2017/745 (MDR) [9], which has finally come into force on May 26, 2021.

1.2 Objective of the thesis and method approach description

1.2.1 Objective

The objective of this master thesis is to critically analyze and evaluate the single steps for approval processes associated with stand-alone software as well as software-supported applications in the field of medical devices in comparison to standard medical devices after introduction of the Medical Device Regulation (EU) 2017/745 (MDR) [9]. The focus of the evaluation will be set on market access and risk assessment of medical device software in order to examine and discuss in more detail the following questions, derived from the introductory considerations presented:

- From a regulatory and safety perspective, how does the presence of software-based applications in the medical device sector affect manufacturing and approval processes when considered in the light of the new Medical Device Regulation (EU) 2017/745 (MDR) [9]?
- To what extent can approval processes be optimized from a safety and regulatory perspective?

1.2.2 Method approach

As a first step, a short overview of the eHealth technologies currently available and used in the medical sector and their potential applications will be given to introduce the digital landscape within which this master thesis is situated (Section 2). The thesis itself will be limited to applications which were either used as stand-alone software or in combination with a medical device, to frame the scope of this document.

As a second step and in order to get an overview of the complexity of the related regulatory landscape dealing with the topic of software and software-supported applications, the legally important sources such as regulations, directives, guidelines and supportive documents that are relevant for the assessment and approval of software products in the medical device sector (Section 3), will be identified and compiled.

These are representing the basic performance tools that are relevant for development and approval processes and are supportive to answer the questions.

From the point of view of a safety perspective, in the main part of this master thesis (Section 4), the individual steps required for approval and maintenance of software-supported applications in the field of medical devices are to be investigated in more detail, critical points are to be identified and evaluated, and possible solutions are to be developed. On the basis of the results of these considerations, the questions raised in Section 1.2.1 will be discussed and a final conclusion will be drawn at the end.

The following systematic is to be used for this purpose:

First of all, the general procedure of the process to place a medical device on the market shall be explained. This is followed by a step-by-step analysis of the individual process steps from the perspective of a risk evaluation.

It will be shown and evaluated which requirements have to be met and which special aspects have to be taken into account in order to fulfill the obligations for stand-alone software as well as software-supported applications in the field of medical devices within the framework of the existing legal requirements and what measures have to be taken for the maintenance of the market authorization. Since this topic is very wide-ranging and a complete analysis would go beyond the scope of this master thesis, the focus will be laid on regulatory processes, risk management and usability of devices with software. Only the processes in the European Union, represented by the conditions in Germany, will be considered for the evaluation of the regulatory procedures. Furthermore, considerations of clinical evaluations and in vitro diagnostic medical devices will also not be part of this thesis. Only the main legal requirements for this kind of products will be mentioned for completeness.

The safety relevant problems and critical parameters that may occur in the individual steps of development, launch and maintenance process of software used for medical purposes will be shown. These issues are to be identified, evaluated, and possible solutions shall be identified and discussed.

To what extent the currently existing legal framework and requirements for placing on the market and the use of digital technologies are sufficient, or whether additions or adjustments would be beneficial in certain areas, will be discussed in a final review.

Finally, a short outlook will be given and discussed on the opportunities and possibilities that digital technologies can offer to significantly improve the medical care situation, especially for specific patient groups, e.g. such as the elderly or disabled, and where there is currently still a need for improvement in order to make the technology usable for everyone (Section 6).

2 E-HEALTH - LANDSCAPE OF DIGITAL TECHNOLOGIES IN HEALTHCARE

The progress that the medical sector has made in recent decades, not at least as a result of advances in technology, is immense. In the industrialized countries in particular, demographics have developed in such a way that average life expectancy continues to increase [10]. As the population ages, the number of patients suffering from age-related diseases is increasing at the same rate. As a result, the need for adequate care is also steadily growing, placing an ever-greater burden on the healthcare system. Especially in rural areas, where medical care is already partly problematic due to long distances and a lack of medical specialists, there is a need for alternative options to improve the existing situation, also with regard to the future. This is why this objective, which is to sustainably improve healthcare for the population through a more efficient healthcare policy, was included in the German federal government's research and innovation policy in 2018. This concept, known as the “Hightech Strategy 2025” [11], [12], is based mainly on the implementation and expansion of digitalization in many areas of society, including the medical, pharmaceutical and healthcare sectors.

In this context, the term "eHealth", synonymous with "electronic Health", comes up frequently. But what does it actually mean? A first approach is already given in the introduction of this thesis (see Section 1), but a concrete definition is difficult, since the digital world is subject to permanent change and the distinction between eHealth and other areas of digitalization in the healthcare sector such as Telemedicine is sometimes fluid. eHealth is seen on the one hand as the sum of all electronically supported systems or activities in the healthcare system that are used to collect, evaluate and forward medical information using non-standard techniques, or even as a superordinate term for all electronic applications in the medical sector [13]. What all definitions have in common, however, is that eHealth represents a summary of all existing measures and applications in the healthcare system that, at their core, rely on and use modern information and

communication technologies (ICT) to support treatment and care of patients [14]. As part of the so-called Telematics Infrastructure (TI), digital applications are becoming increasingly connected through interoperability, i.e. the exchange and storage of data for medical application purposes, with the aim of making medical information such as collected digital measured data or a patient's medical and treatment history more quickly and comprehensively visible and available to co- and follow-up treating, professionals and enabling patients to more easily identify the scope of data stored about them and to actively participate in the medical treatment processes tailored to them.

To provide an overview of what exactly is meant by digital technologies or eHealth in healthcare, respectively, which is included in the Telematic Infrastructure, in the following sections the most important applications will be introduced.

2.1 Mobile Health (mHealth) apps

Mobile health, also known as "mHealth" for short, is a branch of eHealth applications. Mobile Health is characterized by the fact that it uses apps and software applications that are made available on mobile devices such as smartphones, tablets, but also desktop PCs or as web applications for browsers. A large number of so-called "health apps" are freely available via appropriate app stores.

The majority of general health apps do not fall into the "medical app" category. The target users of these apps are health-conscious users who are looking for ways to inform themselves, prevent diseases, and promote health. Although these apps must meet specified requirements from the development side, particularly with regard to data security, e.g. the "Security requirements for digital health apps" guideline published by the Federal Office for Information Security (German: Bundesamt für Sicherheit in der Informationstechnik, BSI) in 2020 [15], which app developers should use as a guideline for the development of secure apps. However, more and more apps are also being developed for special medical indications that focus on people with certain medical disorders.

The borderline between health apps and "real" medical apps is becoming smaller and smaller due to the increasing number of app developments, and the issue of the intended purpose, data protection, and usability is thus coming more and more into focus, as a clear distinction is becoming more and more difficult due to the variety of applications. [16]

Unlike regular health apps, apps that support a specified medical indication can be marketed as medical devices and be subject to prescription by physicians if they fulfill their intended purpose and meet regulatory requirements. In Germany, mHealth apps classified as digital medical devices are referred to as "digital health applications (German: Digitale Gesundheitsanwendungen, DiGAs)" [17]. Like all medical devices, these are brought to market by the manufacturers themselves after they have been subjected to the tests and certifications required by the regulatory framework. DiGAs are also subject to a final evaluation process by the German Federal Institute for Drugs and Medical Devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), the so-called "Fast-Track Procedure", in which the requirements to be met under the regulations are checked within a period of three months. The BfArM has also established a public directory, listing those DiGAs that have successfully completed the fast-track procedure [18; 19]. These are then prescribable by physicians, which was made feasible by the coming into force of the Digital Health Care Act (German: Digitale-Versorgung-Gesetz, DVG) [20] on December 19, 2019. As a general rule, these are designed for the private sector, i.e., they are following a patient-centered approach in terms of being usable by the patients themselves and tailored to the needs in a variety of disease patterns and application areas (e.g., diabetes, obesity, psychotherapy, physiotherapy). On the one hand, the use of the apps can contribute to the treatment of their disease, but on the other hand, it can also encourage their own health competence and health awareness, as they are actively involved in the treatment process and are able to learn in a simple way how to better deal with their impairments and thus achieve improvements in their condition.

In this context, the German Federal Ministry of Health (German: Bundesministerium für Gesundheit, BMG) emphasizes that it still foresees a huge potential for establishing new possibilities in diagnosis and therapy, which can be related to the combination of medical devices with software and sensoric measurement methods [2; 17].

2.2 Wearable health devices

Wearable health devices such as fitness trackers, smartwatches or other sensors attached to the body are assigned to the mHealth area. These are electronic devices that are worn on the body and are mainly used to monitor vital functions. A basic distinction can be made here between two areas of application. On the one hand, they are used to check and monitor one's own activity and fitness. In the medical field, they provide physicians with important data that can be used to monitor a patient's condition, make diagnoses or determine further treatment. [21]

2.3 Electronic medical records (EMRs)

The electronic medical record refers to the data recorded within a practice or clinic by medical professionals, i.e. it is the digital form of the medical record previously kept in paper form in practices and hospitals and thus a mere documentation tool for use within the practice or hospital. The advantages of the digital version over the paper version are that health data and parameters are easier to compare and track, making it easier and more accurate to assess the quality of treatment. [22]

2.4 Electronic health records (EHRs)

The comparison with other countries has shown that the otherwise very efficient German health care system still has deficits [6; 7; 8], which are unfavorable for patients and also increase the costs of the health care system, for example through duplicate or inefficient treatments, threaten the safety of patients, e.g. through parallel medication by different physicians and the resulting possible drug interactions, and thus also have a negative

impact on the general quality of care. This is widely due to the still inadequate interoperability of the systems of the individual stakeholders in the healthcare system. [23] As part of the measures resulting from the priorities of the German government's "High-Tech Strategy 2025" [11] to improve the health care situation and promote digitalization, the Appointment Service and Care Act (German: Terminservice- und Versorgungsgesetz, TSVG) [24] was adopted and came into force on May 10, 2019. It introduced far-reaching changes to Book Five (V) of the German Social Code (German: Buch Fünf Sozialgesetzbuch, SGB V) [25]. Among other things, the health insurances were obliged to provide their members with electronic health records from January 1, 2021. As early as the end of 2018, the requirements for the electronic health record were defined and set out in guidelines to ensure its interoperability by the Gesellschaft für Telematikanwendungen der Gesundheitskarte mbH (gematik GmbH), which is a company for telematics applications for the electronic health card. The patient himself determines the data in his EHR, can enter and delete data from the various physicians, enter his own data and grant or revoke access rights. The use is on a voluntary basis, i.e. there is no obligation to enter the data. The patient alone decides on the extent of use. He also decides whether the data may be passed on and to whom. [26, 27]

2.5 Telemedicine

Telemedicine is the use of digital technology and telecommunications to treat and inform patients who are not in the same location as physicians, pharmacists or other healthcare professionals such as therapists. Tasks such as diagnosis, monitoring and therapy, as well as advice sessions and health training, can be delivered through this format and add value in areas and regions where there are gaps in care.

2.6 Home medical devices

Due to the aging population and the resulting cost explosion, as well as the reimbursement of health care costs and the shift of follow-up care from hospitals to the

private sector, home medical devices are playing an increasingly important role. The term Home Use Medical Devices covers devices that can be used by patients themselves in their home environment without the assistance of medical staff or with the help of, for example, a nursing service. This ranges from medical devices with digital dosing aids such as infusion pumps, devices for respiratory use such as oxygen devices or inhalation devices, to devices for monitoring, the monitoring of vital functions and parameters that can help the physician in diagnosis and therapy, and many more. Developments, particularly in the digital medical device space, are contributing to a comprehensive expansion of options available to users or patients in the home. Many tasks that were otherwise performed in the course of follow-up care or monitoring of patients by hospitals or doctors' offices, as well as nursing care, are now being shifted to the private sector in a variety of ways and thus largely left to the personal responsibility of users. [28]

The problem here lies primarily in developing the products qualitatively in such a way that they can be used safely and effectively by medical laypersons themselves, without the need for medical professionals to provide assistance. The human factor is the biggest problem in these developments. On the one hand, the usability for the user must be given. The acceptance of the medical device and the willingness to use it depend heavily on this. In addition, suitable measures must be taken to prevent errors in use, such as incorrect settings of the devices, doses that are too high or too low, or misuse for other purposes. [28]

The risk management of these products in particular requires a great deal of attention. Since the risk potential is particularly high in this area due to the complexity of software and also the "human" factor, which is difficult to calculate, an evaluation of the safety aspects of digital medical device applications will take place in Section 4.5 and the following sections (Risk Management).

3 REGULATORY LANDSCAPE RELEVANT FOR DIGITAL MEDICAL DEVICE TECHNOLOGY

The regulatory landscape in the field of medical devices is very diverse and both, devices and software for medical purposes, are strictly regulated. Numerous laws, regulations, directives, guidelines, implementing decisions and other supportive documents, which are constantly updated and must or should be followed, confront manufacturers and authorities with major challenges. In this chapter an overview of the most significant documents for the current regulation of medical devices as well as stand-alone and combined software applications shall be presented.

3.1 European Union

From the very beginning, the European Union was conceived as an economic union, with the aim of removing trade restrictions between countries as far as possible, allowing free exchange and distribution of products, and thus creating conditions to ensure the supply of goods of equal quality to each country within the Union. In the course of harmonization of the individual national legislations, an extensive catalog of legal requirements, directives and standards has been created over time to guarantee a consistent and high quality and safety of medical devices produced within the European Union, regardless of the country in which they are produced. With the introduction and entry into force of Regulation (EU) 2017/745 (MDR) on medical devices [9] on 26 May 2021, which replaced Council Directive 93/42/EEC (MDD) [29] and Council Directive 90/385/EEC (AIMDD) [30], and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) [31], which replaced Council Directive 98/79/EEC (IVDD) [32], the requirements for medical devices within Europe have once again been fundamentally tightened, which is also reflected in the new creation and revision of numerous documents. An overview of the most significant documents and papers for the current regulation of medical devices as well as stand-alone and combined software applications in the European Union is shown in Table 1.

Table 1: Current documents with relevance for development and approval of digital technologies in the medical devices sector (European Union)

European legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
Regulation	Regulation (EU) 2017/745 (MDR)	Medical devices	[9]
	Regulation (EU) 2017/746 (IVDR)	In vitro diagnostic medical devices	[31]
	Regulation (EC) No 726/2004	Authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA)	[33]
	Commission Implementing Regulation (EU) 2021/2226	Rules for the application of MDR as regards electronic instructions for use of medical devices	[34]
	Commission Implementing Regulation (EU) 2021/2078	Rules for the application of MDR as regards the European Database on Medical Devices (Eudamed)	[35]
	Regulation (EU) No 1025/2012	European standardisation	[36]
Directive	Council Directive 93/42/EEC (MDD) Of note: No longer in force, End of validity: 25/05/2021	Medical devices	[29]
	Council Directive 90/385/EEC (AIMD) Of note: No longer in force, End of validity: 25/05/2021	Active implantable medical devices	[30]
	Directive 98/79/EC (IVMD)	In vitro diagnostic medical devices	[32]
	Directive 2001/83/EC	Community code relating to medicinal products for human use	[37]
Guidance	EMA/CHMP/QWP/BWP/259165/2019 (Guideline)	Quality documentation for medicinal products when used with a medical device	[38]
	Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies Rev.2 EMA/37991/2019	Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations MDR and IVDR	[39]
	Commission Implementing Decision (EU) 2021/1182	Harmonised standards for medical devices drafted in support of MDR	[40]

Table 1: Current documents with relevance for development and approval of digital technologies in the medical devices sector (European Union)

European legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
Guidance	Commission Implementing Decision (EU) 2022/6	Harmonised standards for biological evaluation of medical devices, sterilisation of health care products, aseptic processing of health care products, quality management systems, symbols to be used with information to be supplied by the manufacturer, processing of health care products and home light therapy equipment	[41]
	MDCG 2018-1 Draft guidance. Version 2	Basic UDI-DI and changes to UDI-DI	[42]
	MDCG 2018-5 Guidance	UDI Assignment to Medical Device Software	[43]
	MDCG 2019-11 Guidance	Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR	[44]
	MDCG 2019-16 Rev.1 Guidance	Cybersecurity for medical devices	[45]
	MDCG 2020-1 Guidance	Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software	[46]
	MDCG 2021-24 Guidance	Classification of medical devices	[47]
	MEDDEV 2.1/6 Guidance	Qualification and classification of stand alone software	[48]
	Background note on the use of the Manual on borderline and classification for medical devices under the Directives.		[49]
	Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices. Version 1.22 (05-2019).		[50]
Standard	IEC 60601-1-6:2010+AMD1:2013+AMD2: 2020 CSV (Consolidated version). International Standard	Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	[51]
	IEC 62304:2006+AMD1:2015 CSV (Consolidated Version). International Standard	Medical device software - Software life cycle processes	[52]

Table 1: Current documents with relevance for development and approval of digital technologies in the medical devices sector (European Union)

European legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
Standard	IEC 62366-1:2015+AMD1:2020 CSV (Consolidated Version). International Standard	Medical devices - Part 1: Application of usability engineering to medical devices	[53]
	IEC 82304-1:2016 . International Standard	Health Software - Part 1: General requirements for product safety	[54]
	ISO 9241-110:2020	Ergonomics of human-system interaction - Part 110: Interaction principles	55
	ISO 13485:2016(en)	Medical devices — Quality management systems — Requirements for regulatory purposes	[56]
	ISO 14971:2019(en)	Medical devices — Application of risk management to medical devices	[57]
	ISO/TR 24971 Technical Report	Medical devices — Guidance on the application of ISO 14971	[58]

3.2 Germany

The update of the European legislation for medical devices, has a far-reaching impact on the legislation in Germany. Until the introduction of Regulation (EU) 2017/745 (MDR) [9] on 26 May 2021, the law laid down in Council Directive 93/42/EEC (MDD) [29] and Council Directive 90/385/EEC [30] had to be transposed into national law, which was done by enacting the Medical Devices Law (German: Medizinproduktegesetz, MPG) [59]. Due to the successful conversion of the European law for medical devices into a regulation, the obligation to transpose it into national law was no longer applicable, since regulations within the European Union are per se directly binding and thus national implementations such as the German Medical Devices Law (German: Medizinproduktegesetz, MPG) [59] lose their validity.

In order to specify how the requirements of the MDR are to be implemented and applied, the Medical Device Law Implementing Act (German: Medizinprodukterecht-Durchführungsgesetz, MPDG) [60] was enacted in Germany, which not only describes the implementation procedure but also outlines the remaining national options within the regulatory processes. This has resulted in a national regulatory framework that is significantly larger when compared to the MPG [59] that has been in force so far.

The following Table 2 shows a compilation of the most important national documents that are currently applicable in Germany for the development and approval of medical devices as well as digital technology in this sector. Again, it should be noted that the table can only show a small section of the regulatory landscape and does not claim to be comprehensive.

Table 2: Current documents with relevance for development and approval of digital technologies in the medical devices sector (Germany)

German legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
National law	Gesetz zur Durchführung unionsrechtlicher Vorschriften betreffend Medizinprodukte (Medizinprodukterecht-Durchführungsgesetz - MPDG) vom 28. April 2020 (BGBl. I S. 960), zuletzt geändert durch Artikel 3f des Gesetzes vom 28. Juni 2022 (BGBl. I S. 938) [German]: issued on: 28.06.2022	Implementation of EU regulations relating to medical devices	[60]
	Gesetz zur Anpassung des Medizinprodukterechts an die Verordnung (EU) 2017/745 und die Verordnung (EU) 2017/746 (Medizinprodukte-EU-Anpassungsgesetz – MPEUAnpG) vom 28. April 2020 [German]	Alignment of medical device law with Regulation (EU) 2017/745 and Regulation (EU) 2017/746	[61]
	Gesetz über Medizinprodukte Medizinproduktegesetz (MPG) [German] Of note: No longer in force, End of validity: 25/05/2021	Medicinal products	[59]

Table 2: Current documents with relevance for development and approval of digital technologies in the medical devices sector (Germany)

German legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
National law	Gesetz für sichere digitale Kommunikation und Anwendungen im Gesundheitswesen sowie zur Änderung weiterer Gesetze vom 21. Dezember 2015 (E-Health Gesetz), in force: 28.12.2015	Secure digital communications and applications in healthcare, amendment of other laws	[62]
	Gesetz für schnellere Termine und bessere Versorgung (Terminservice- und Versorgungsgesetz – TSVG) vom 6. Mai 2019, in force: 10.05.2019	Faster appointments and better care	[24]
	Gesetz für mehr Sicherheit in der Arzneimittelversorgung vom 9. August 2019 (GSAV), in force: 15.08.2019	Safety in the drug supply	[63]
	Gesetz für eine bessere Versorgung durch Digitalisierung und Innovation (Digitale-Versorgung-Gesetz – DVG) vom 9. Dezember 2019, in force: 18.12.2019	Law for better care through digitalization and innovation	[64]
	Gesetz zum Schutz elektronischer Patientendaten in der Telematikinfrastruktur (Patientendaten-Schutz-Gesetz – PDSG) vom 14. Oktober 2020, in force: 19.10.2020	Protection of electronic patient data in the telematics infrastructure	[65]
	Gesetz zur digitalen Modernisierung von Versorgung und Pflege (Digitale-Versorgung-und-Pflege-Modernisierungs-Gesetz – DVPMG) vom 3. Juni 2021, in force: 08.06.2021	Digital modernization of supply and care	[66]
National regulations and standards	Verordnung zur Anpassung des Medizinprodukterechts an die Verordnung (EU) 2017/745 und die Verordnung (EU) 2017/746 (Medizinprodukte-EU-Anpassungsverordnung – MPEUAnpV) vom 21. April 2021 [German], in force: 27.04.2021	Alignment of medical device law with Regulation (EU) 2017/745 and Regu-lation (EU) 2017/746	[67]
	Verordnung über das Errichten, Betreiben und Anwenden von Medizinprodukten (Medizinprodukte-Betreiberverordnung - MPBetreibV) vom 29 Jun 1998, zuletzt geändert durch Art. 7 V vom 21 Apr 2021 [German]	Installation, operation and use of medical devices	[68]

Table 2: Current documents with relevance for development and approval of digital technologies in the medical devices sector (Germany)

German legislation, guidance and standards			
Type	**Document**	**Item**	**Source**
National regulations and standards	Verordnung über die Meldung von mutmaßlichen schwerwiegenden Vorkommnissen bei Medizinprodukten sowie zum Informationsaustausch der zuständigen Behörden (Medizinprodukte-Anwendermelde- und Informationsverordnung - MPAMIV)	Notification of suspected serious incidents involving medical devices and for the exchange of information between the competent authorities	[69]
	Verordnung über das Verfahren und die Anforderungen zur Prüfung der Erstattungsfähigkeit digitaler Gesundheitsanwendungen in der gesetzlichenKrankenversicherung (Digitale Gesundheitsanwendungen-Verordnung - DiGAV) vom 8. April 2020	Procedure and requirements for reviewing the eligibility for reimbursement of digital health applications in the public health insurance system.	[70]
	Technische Richtlinie TR-0316: Anforderungen an Anwendungen im Gesundheitswesen. Teil 1: Mobile Anwendungen. Version 2.0. 18.05.2022	Requirements for healthcare applications	[71]
	Technische Richtlinie TR-0316: Anforderungen an Anwendungen im Gesundheitswesen. Teil 2: Web-Anwendungen. Version 1.0. 18.05.2022	Requirements for healthcare applications	[72]
	Technische Richtlinie TR-0316: Anforderungen an Anwendungen im Gesundheitswesen. Teil 3: Hintergrundsysteme. Version 1.0. 18.05.2022	Requirements for healthcare applications	[73]

4 EVALUATION OF REGULATORY PROCESSES FOR SOFTWARE BASED APPLICATIONS

As already described in detail in the previous chapters, the regulation of medical devices in the European Union is represented and implemented by a diverse set of regulations (see Table 1), which are also accompanied by corresponding procedural guidelines and standards for implementation on the national side, as shown in the example of Germany (see Table 2). These apply to all medical devices to be placed on the market. The medical device world is a wide-ranging field. Therefore, only a small area of this complex structure can be examined in more detail.

This chapter will therefore focus on the most safety relevant development and regulatory processes that are necessary for bringing software-based or software-supported medical devices to market and putting them into operation. In a step-by-step approach, the individual phases will be examined, problems identified and discussed (cf. Section 1.2, Objective and method approach). The analysis is based on the Medical Device Regulation (EU) 2017/745 (MDR) [9] of April 5, 2017, which came into force on May 26, 2021, and the implementation procedure derived from it, the German Medical Device Law Implementing Act (German: Medizinprodukterecht-Durchführungsgesetz, MPDG) [60] of April 28, 2020 (amended on June 28, 2022). These two documents are very structured and contain all the specifications required for the registration and market launch of medical devices.

4.1 Qualification of Software as Medical Device

4.1.1 Definition and evaluation

In order to be able to make a statement as to whether software can be considered without limitation as a medical device requiring regulation, it is first necessary to clarify what the term "medical device" actually means.

Different software groups are to be considered here:

- Software that is a medical device in the sense of a standalone application
- Software that is part of a medical device (embedded software)
- Software that is itself a medical device, but also an accessory of a medical device

4.1.1.1 Definition according to Medical Device Regulation (EU) 2017/745

With the introduction of the MDR, as already mentioned, the requirements for medical products were once again fundamentally revised and in some cases tightened in contrast to the legal framework that applied before. This affects digital software applications in particular, which are becoming increasingly important.

Thus, the Medical Device Regulation (EU) 2017/745 (MDR) [9] also provides a slightly modified definition for the term "medical device" in Article 2 (1):

> *"[...] 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*
>
> *— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
>
> *— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
>
> *— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
>
> *— providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. [...]" [9]

In the first paragraph of this definition, software is now explicitly mentioned as a potential medical device. The formulation "*[...] any instrument, apparatus, appliance, software, implant, reagent, material or other article [...]*" [9] implies, that only physical objects can be declared as medical devices. At the same time, the MDR also lists the purpose-related requirements that must be fulfilled in order to comply with this function. According to the definition of the MDR, medical devices explicitly exclude items that are considered protective devices in the widest sense. The listing of specific medical purposes illustrates this clearly. While the prevention of diseases is listed here as one of the primary objectives, the purpose of prevention in connection with injuries or disabilities is not mentioned and accordingly is not placed under the regulatory obligation of the MDR. [74]

However, the classification of digital media, as compared to medical devices, is not always unambiguous, since software does not always have to be an independent, stand-alone medical device, but can also assume a function in combination with another device that is already classified as a medical device. Software does not thus necessarily have to represent a medical device requiring regulation. The definition as a medical device to be regulated therefore logically requires a very precise statement about the intended purpose in order to be able to carry out this evaluation. This allocation for software cannot necessarily be derived from the definition of MDR itself. [75]

Furthermore, it is apparent that in the course of updating the legislation for medical products, the significance of software is currently being raised to a higher level. What used to be regarded primarily as a supportive medium is now being elevated to the status of a potential full-value medical product.

If a comparison is made between the previously relevant Council Directive 93/42/EEC (MDD) [29] and its succeeding MDR [9], it can be seen that software now also occupies a different place in the consideration of medical devices. This was initially classified under:

> *"[...] including the software necessary for its proper application [...]* " [29]

Now it is mentioned on an equal basis under the designation "software" next to the terms defining the medical devices. The MDR no longer differentiates between the individual types of software, i.e. stand-alone software, control/embedded software or software as an accessory, as was still the case under the old regulation in the MPG [59]. All types of software are included under a unified software term and can be defined as a medical device if the requirements for safety and performance are met and a medical purpose and intended use can be proven. *"[...] instrument, apparatus, appliance, software [...]*" [9]

4.1.1.2 Definition according to MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

As just noted, the requirements for medical devices specified in the MDR still leave some room for interpretation, especially in the context of the qualification of software as a medical device. In order to provide manufacturers with assistance in this matter, in 2019 they were provided with the guideline "*MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR*" [44], a document specifically aimed at the qualification and classification of software but not legally binding. The document is merely a recommendation that can be used for clarifying discussions with the reviewing institutions such as Notified Bodies or BfArM. [76]

In the MDCG 2019-11 [44] the following definition for software as medical device can be found:

"*Medical Device Software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a medical device in the MDR or IVDR, regardless of whether the software is independent or driving or influencing the use of a device.*" [44]

This definition focuses merely on the intended medical purpose, irrespective of the use, whether it is standalone software or control software. The MDR, on the other hand, does not make any distinction and does not specify the term "software", but does include the intended use in the evaluation.

The inclusion of the term "software" in the definition of medical devices also takes into account the advancing digitalization in society, especially in the medical sector, and assigns greater importance to software-based applications. The latter are increasingly coming into the focus of manufacturers and regulatory institutions, because even, and in particular in the case of software-supported applications, numerous aspects, especially in the area of safety and usability, must be taken into account during development, which determine whether and to what extent software can be considered a medical device and as such must be subject to the regulatory framework. The medical device market is highly competitive. Consequently, the acceptance of the devices by the user also plays a major role. For this purpose, not only the safety of the medical device, but also the ease of use must be ensured.

4.1.2 Interim conclusion

Due to an increasing number of software-based applications in the healthcare sector, these are also becoming more and more important and visible in the regulatory area. In the MDR a slightly changed definition for medical devices is observed, compared to the previous documents in force, e.g.. Software is listed in the sense of a high-level and full-value medicinal product, after it was still largely seen as a supporting aid in former times (cf. Section 4.1.1). This increase in value and importance also has an impact on the development and regulatory process and thus becomes much more important for

manufacturers and regulatory stakeholders, as more attention must now be paid to safety aspects and usability, and higher standards must be applied in general for placing products on the market. It can also be concluded that the qualification of software as a medical device cannot necessarily be derived alone from the MDR definition of a medical device presented in Annex I [9]. This requires a more precise definition of the intended purpose.

In contrast to the previous legislation, implemented by the MPG [59], the MDR [9] no longer makes a distinction between standalone software and integrated (control) software. This is generally included under the term "software", so that it can be expected that integrated, or "embedded" software can also be considered a medical device. As embedded software, however, it is seen as forming a unit with the associated medical device and is assumed to follow the same medical purpose, so that it is included under the definition of the overall product and must undergo the conformity assessment procedure together with it. However, the question arises as to whether such integrated software can really only be regarded as control software and thus as belonging to the type of general software, or whether, through its use in a medical device that follows a medical intended purpose, it does not also contain this intended purpose with the risks for safety that can be assigned to it, which would also have to be checked by a corresponding separate conformity assessment procedure. Standalone software as an app as well as software that functions as an independent accessory for a medical device will be in any case subject to its own conformity assessment procedure. [77]

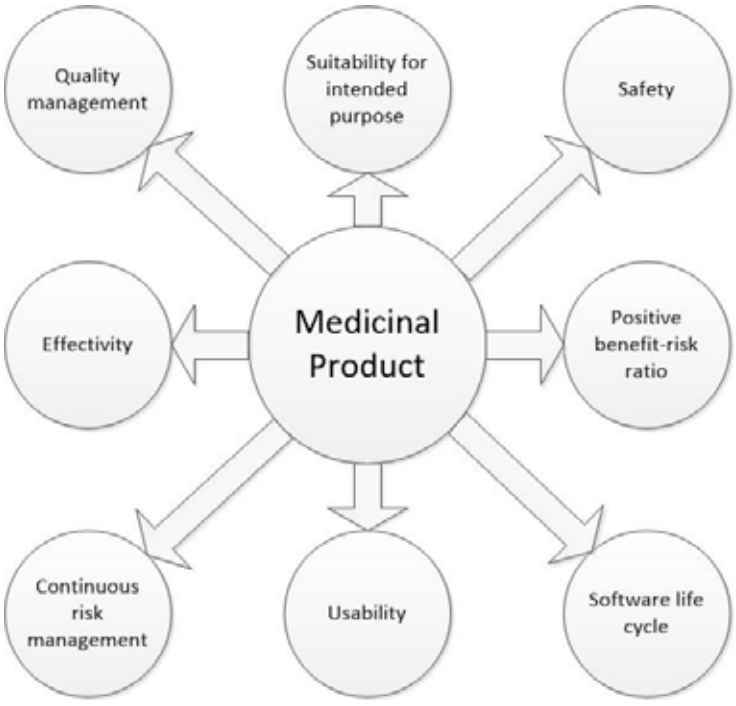
4.2 Development and life cycle of a medical device

The basis for the development of medical devices is the existing framework of legislation and harmonized standards (as presented in Section 3 for the European Union and Germany). Unlike medicinal products, which are approved by the competent federal authorities (in Germany: BfArM (German Federal Institute for Drugs and Medical Devices) for chemical medicinal products, and PEI (Federal Institute for Vaccines and Biomedical

Drugs) for biological medicinal products) or centrally in the European Economic Area by the EMA (European Medicines Agency), in the case of medical devices the manufacturer alone is responsible for the market entry of his product and must provide evidence that his product meets all the requirements which have to be fulfilled. For products that have a certain risk potential, organizations (notified bodies) designated by the responsible state authorities carry out the conformity assessment procedure and perform supervisory tasks of products and manufacturers.

4.2.1 General Requirements for the Regulation of Medical Devices

Products that are to be developed and placed on the market must meet certain requirements. The MDR [9] lists the essential disciplines and criteria in Annex I, which are also reflected in the German Medical Devices Law Implementation Act (German: MPDG) [60]



Source: Self-developed graphic based on information from MDR [9] and MPDG [60] (created with Microsoft® Visio Premium 2010)

Figure 1: General requirements for medical devices according to MDR and MPDG

4.2.2 Description of the life cycle of a medical device

The life cycle of a medical device covers the entire range, from the initial consideration of the product, through market launch, to decommissioning. The Medical Device Regulation (EU) 2017/745 (MDR) [9] is the European basis for these processes. The individual procedural steps result from the basic requirements for medical devices with regard to quality, performance and safety, as already shown in Figure 1. In the MDR itself, the life cycle of a product is mentioned and referenced in several places. This results in some mandatory processes and activities of the manufacturer that must be maintained throughout the whole life cycle of the product. These are:

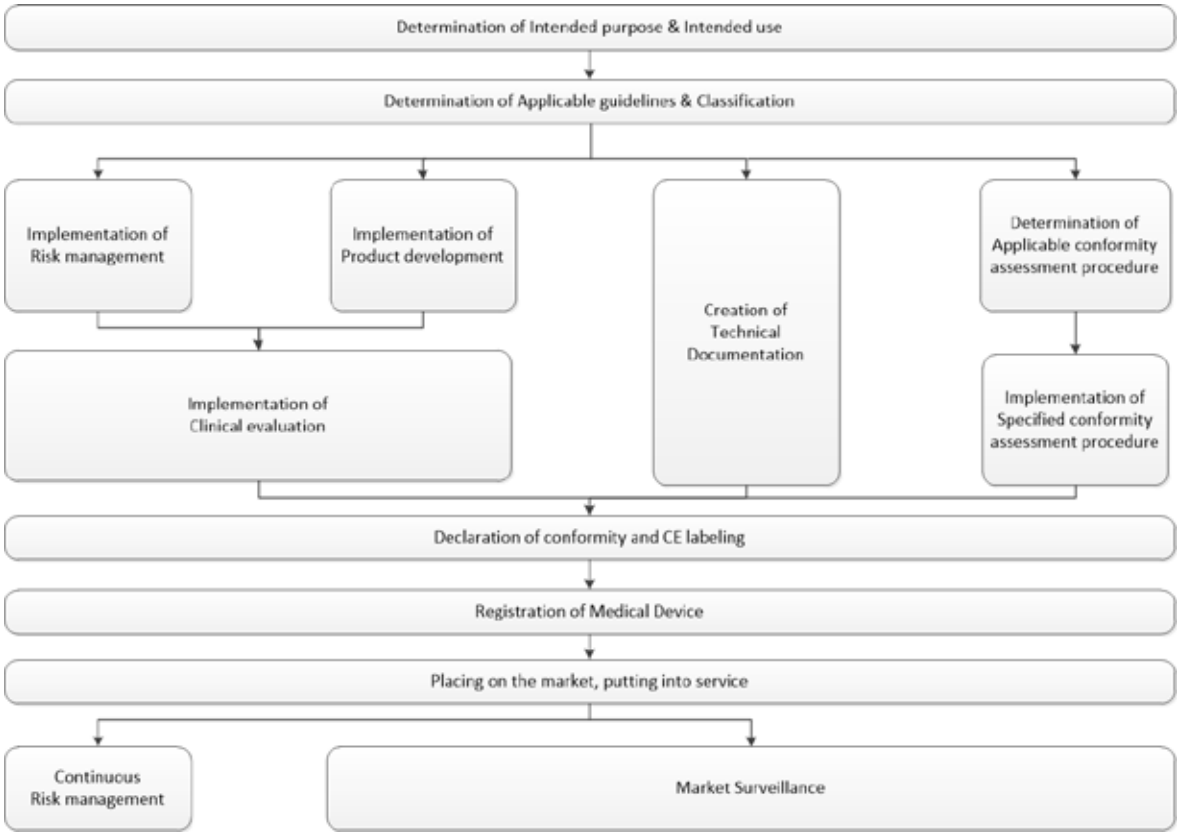
- Article 61: Continuous update of clinical evaluation and update
- Annex I: Continuous risk management
- Annex IX: Establishment and maintenance of a quality management system
- Annex X: Application for a conformity assessment procedure from a Notified Body

Another prerequisite for placing a medical device on the market and operating it within Europe is the CE label. This certifies that the product has been developed in accordance with the requirements laid down in the MDR as well as with all other regulations laid down in Europe for obtaining the mark and that it conforms to them. [9, 74] For this purpose, the manufacturer must establish a quality management system that can be used to perform a risk assessment and a clinical evaluation to determine the safety and risk-benefit ratio of the medical device under investigation as part of a so-called conformity assessment procedure. Proof of compliance with the requirements is provided in comprehensive technical documentation.

The need for regulation of medical devices by means of a quality management system is mainly based on the potential risks that the operation of a product may involve. The regulatory procedure for obtaining CE labeling is based on the risk associated with the product in question.

Only for those products that are considered to be harmless to risk can conformity be confirmed by the manufacturer himself. All other products must go through this procedure with the involvement of the so-called "notified bodies", which in the case of Germany are designated and monitored by the ZLG (Zentralstelle der Länder für Gesundheitsschutz bei Arzneimittel und Medizinprodukten). Once the CE label is granted, the product can be registered and placed on the market. After market launch, the manufacturer is obliged to conduct continuous risk management and to monitor the product.

The life cycle of a medical device is shown in Figure 2 in a schematic and simplified form in order to clarify the process.



Source: Graphic freely adapted from: JOHNER, Christian; HÖLZER-KLÜPFEL, Matthias; WITTORF, Sven. Baiswissen Medizinische Software. 3. Auflage. dpunkt.verlag GmbH, Heidelberg. 2021. p.45 [74] (created with Microsoft® Visio Premium 2010)

Figure 2: Life cycle of a medical device

4.2.3 Software life cycle

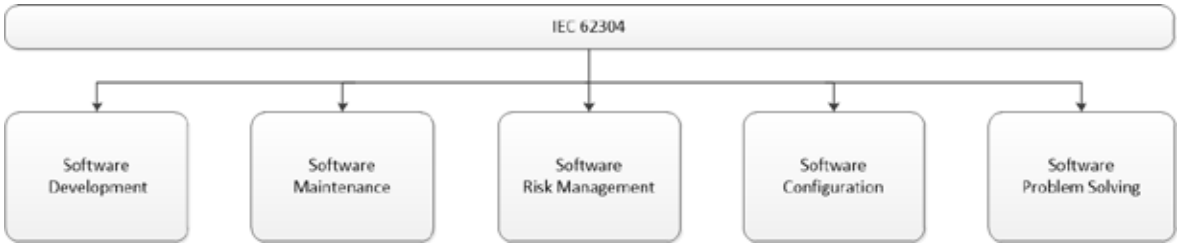
As shown in Figure 1, the software component is an integral part of the medical device world. Whether as stand-alone software or as software integrated into a product, just like "normal" medical devices, software also goes through a life cycle, which is also comparable in the basic requirements. In Annex I, Section 17.2 of the MDR [9], there is also a requirement specifically directed at software that...

"*For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation."*. [9]

This emphasises the requirement to set up a life cycle for software products which includes all processes and activities to develop a safe product. The safety and performance requirements applicable to conventional medical devices are extended for software here by the additional requirement of evaluating IT security, which must be carried out as part of risk management. The MDR, however, is not so much focused on data security as it is on security with regard to patient risks [75], so the requirement for risk management applies primarily to that (cf. Annex I (1) of MDR) [9].

The principles of the software lifecycle are specified for software as a medical device by the two standards IEC 82304-1 [54] and IEC 62304 [52]. The IEC 82304-01 standard [54], which refers generally to healthcare software, i.e. also to software that is not subject to mandatory regulation, addresses the general requirements relating to specification, validation and post-marketing activities. IEC 62304 [52], on the other hand, describes the basic processes of the software lifecycle. However, if the software functions as medical device software, i.e., if it is embedded software as an integral part of a medical device, IEC 82304-1 [54] is not applicable. In the case of embedded software, the standards from the IEC 60601 series of standards [78], which relate to medical electrical equipment, are to be applied instead.

Since there are a large number of standards in this series, only the relevant standard will be referenced in this work if it is applicable. They are also not explicitly mentioned in the tables of Section 3. Based on the requirements of IEC 62304 [52], a development plan must be mandatorily created at the beginning of software development in which the processes to be carried out for implementation of the life cycle are laid down. The development model according to which the tasks are to be performed is not defined and can be determined by the manufacturer. However, the standard specifies five processes that are mandatory for implementation in the life cycle of the software (Figure 3). [74, 79]



Source: Self-developed graphic based on information from IEC 62304 [52] (created with Microsoft® Visio Premium 2010)

Figure 3: Mandatory requirements of software life cycle according to IEC 62304

4.2.4 Interim conclusion

The life cycle of software as a medical device essentially follows the life cycle of a medical device in the conventional sense. However, since it is a digital component, not only the guidelines for conventional medical devices, but also the harmonized standards and guidelines explicitly aimed at this area must be applied. Evidence must be provided that the software not only meets the requirements for medical devices, but that the processes specified or planned for the development of the software also meet the requirements from the harmonized standards. This requires a supplementary evaluation within the framework of the conformity testing, which has to be taken into consideration. The application of the standards depends on the classification of the corresponding software. Therefore, this must already be precisely defined in the development process. In the following, the most important steps of the life cycle of a medical device will be examined and evaluated.

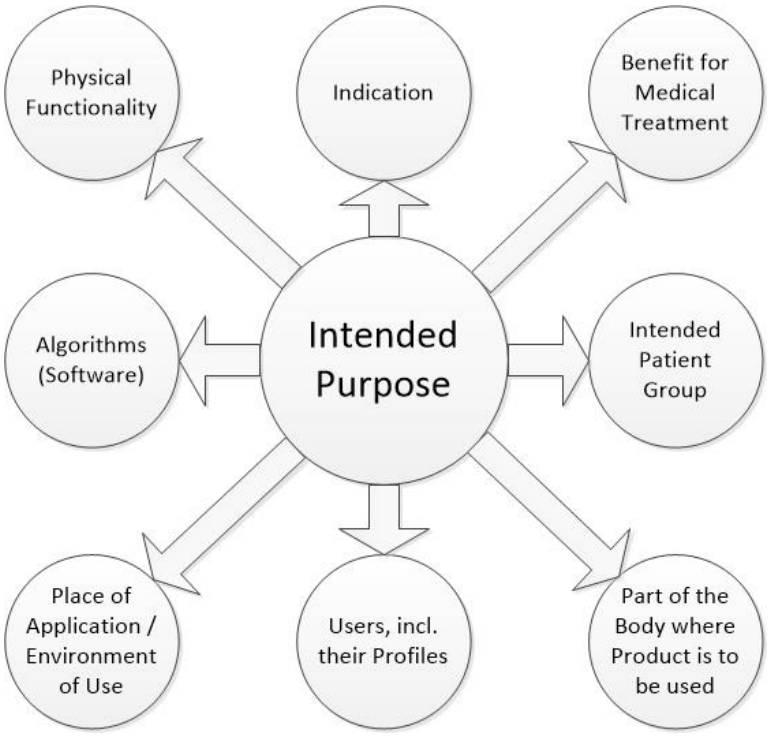
4.3 Qualification - Intended purpose and intended use

4.3.1 Medical device

If a new product is to be developed, the first step is to qualify the product as a medical device, that means to determine whether the planned product is a medical device at all. This assessment also determines which legal requirements are to be used for the development and registration process. The assessment of the status of the product is based on the so-called intended purpose and the intended use. The MDR defines intended purpose in Article 2(12) as follows: "*'intended purpose' means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation*" [9]. Accordingly, the intended purpose is not only relevant for the categorization of a product, but is also used in classification and risk assessment, including usability considerations, as well as in clinical evaluation. [75] Annex II (1.1)a of the MDR also requires for the technical documentation "*[...] a general description of the device including its intended purpose and intended users [...]"*. [9]. The intended purpose of a medical device usually includes the following items:

- Indication
- Benefit for medical treatment, e.g. diagnosis, therapy, etc.
- Intended patient group
- Part of the body where the product is to be used
- Users incl. their profiles
- Place of application / environment of use
- Physical functionality
- algorithms (software)

(cf. [75], Figure 4)



Source: Self-developed graphic based on information from MDR [9] and MPDG [60] (created with Microsoft® Visio Premium 2010)

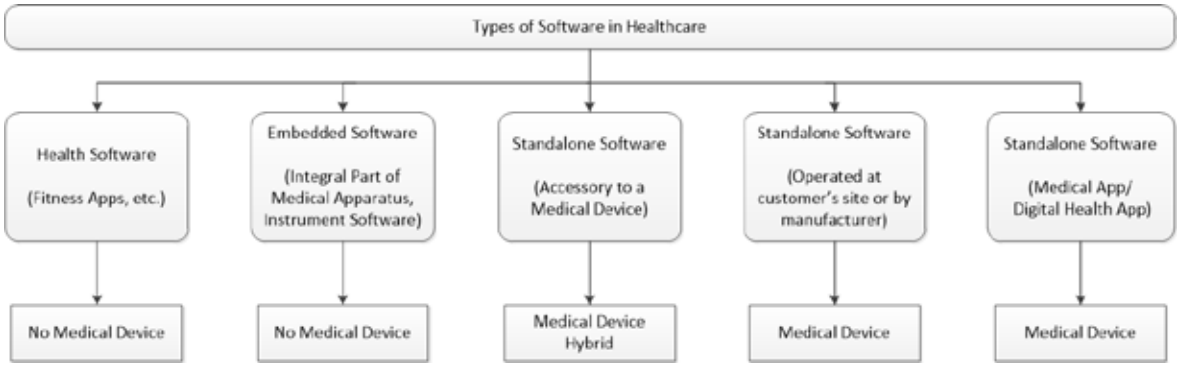
Figure 4: Items of intended purpose for medical devices according to MDR and MPDG

Products that do not meet any of these requirements for a medical intended purpose and intended use, on the other hand, are not considered medical devices.

4.3.2 Medical device software

An indication of whether software is to be defined as a medical device is additionaly provided by the Medical Device Coordination Group's Guidance on Qualification and Classification of Software (MDCG 2019-11) [44] and in EU guideline MEDDEV 2.1/6 [48] which still has relavance in the case standalone software has to be defined. First of all, it must be checked whether the software is medical device software subject to regulation at all. In a first step, the definition from guideline MDCG 2019-11 [44], which is an extract of the MDR together with notes for implementation, must be fulfilled. The MDR explicitly includes software as a potential medical device in its definitions in Art.1(2) and by

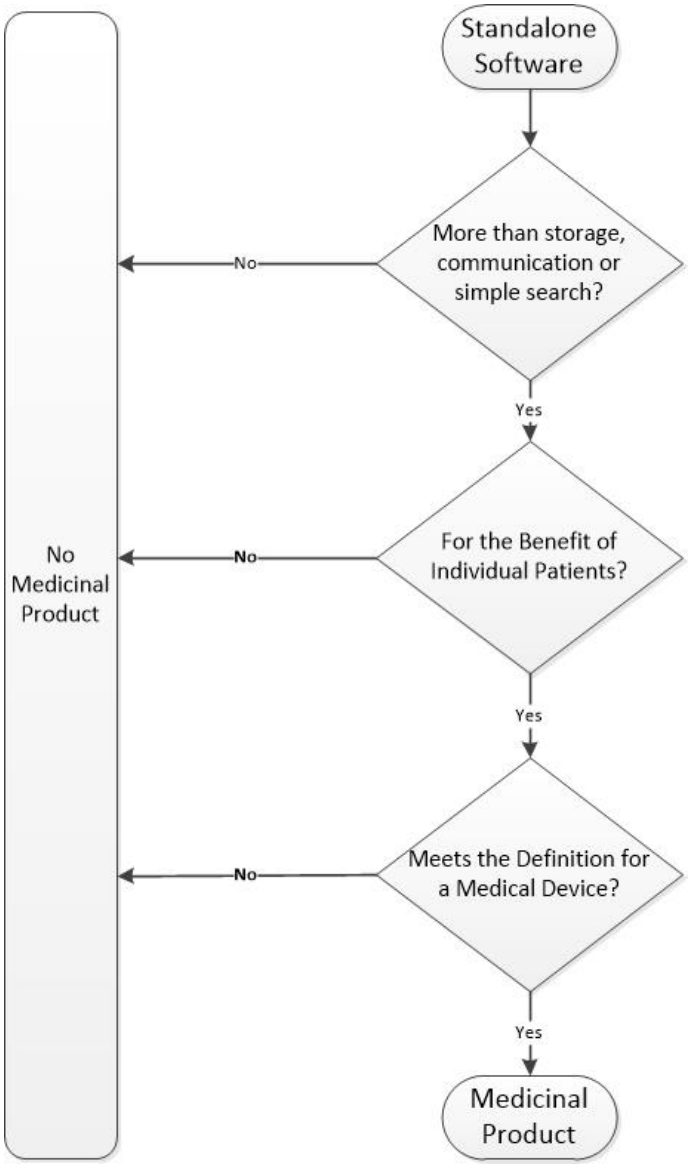
classifying it as "active" device in Art.2(4) (cf. Section 4.3.1). If the definition is not met, the software can still fall under the scope of medical devices if the software is qualified as part of a medical device together with the medical device as "embedded" software. It then does not fall under the collective term Medical Device Software. In the case of stand-alone software, i.e. software that is operated either at the customer's site, by the manufacturer himself or as an application, e.g. on a mobile phone, it must be checked whether or not the requirements for qualification as medical device software, which result from the intended purpose, are met. In the event of non-compliance, the software is not subject to regulation. A gray area exists, however, where the definition is not clear. This is particularly the case when the assessment must check whether software can do more than just store, communicate or search. The attempt to create clarity here is provided by the so-called Manual on Borderline and Classification [50], which attempts to draw the line between medical device software and software in the true sense. Nevertheless, the final evaluation often remains a matter of interpretation. Another borderline case is stand-alone software, which is operated together with a medical device as its own software, but is not built into it. This is a hybrid form that contains independent components but is defined as a combination product as a medical device. [74, 75] Figure 5 shows, which possible types of software can be found in the healthcare sector.



Source: Graphic freely adapted from: HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. p.152 [75] (created with Microsoft® Visio Premium 2010)

Figure 5: Types of software in the medical device sector

As to demonstrate, which factors influence the precise definition of standalone software, the complex process is presented in Figure 6 in a very simplified manner with a very rough approach.



Source: Graphic freely adapted from: HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. p.153 [75] and MDCG 2019-11 [44] (created with Microsoft® Visio Premium 2010)

Figure 6: Decision tree for identification of software as medical device (simplified)

Software used in the medical environment which lies outside of these regulations because, for example, it is only of a general nature, i.e. it cannot be assigned to a medical purpose or is only used for wellness purposes, for example, cannot be defined as a medical device according to the definition.

4.3.3 Interim Conclusion

The definition of whether a device is a medical device is tied to the regulatory definition of intended purpose and intended use. This is determined for the product by the manufacturer and depends on the formulated intended purpose. The intended purpose is not only a document and part of the technical documentation of the product. It is also reflected in, e.g., the instructions for use, online help for the product, the product's web pages, flyers, etc. [80] However, the MDR can only provide a rough framework. It is relatively easy to identify which products definitely do not fall under the umbrella of medical devices, since the properties and requirements stipulated in the regulations do not apply to them and they may therefore not be defined as such. Some products must inevitably fall under this regulation, as they are per se safety-relevant for patients. The question of the need for regulation does not arise there either. Accordingly, there are only two types of software that could fall under the regulation, software that is operated in a medical device, so-called "integral" software, and standalone software. In contrast to the technical devices used in the medical field, the definition of software is much more difficult. Due to the variety of software applications that have been developed in recent years, the borderline between the individual applications and thus also the medical devices is becoming increasingly unclear. They are approaching each other more and more, partly they overlap in the border areas. The gray area between medical device and medical aid or health application is very large. Since the manufacturer is responsible for declaring the intended purpose and use, he assumes a control function to a certain extent as to what the product can ultimately be marketed as. There is a risk here that insufficient attention is paid to safety-related aspects for the sake of easier marketing.

On the other hand, there is the manufacturer's liability for any damage that may be caused by his product. Here both sides, the legislature as well as the manufacturers, are challenged to use the means available to them sensibly and possibly to create more clarity, especially in this borderline area, in order to be able to guarantee the greatest possible safety and efficiency for the users. Thus, it should be considered whether a declaration of an application that is in this borderline area as a medical device is not the better choice in case of doubt, although the effort to place it on the market is then many times greater. By means of an assessment by the inspection bodies to be consulted in the further course of the project, additional security can be achieved for both the manufacturer and the user.

4.4 Classification

After software has been qualified as a medical device according to the medical purpose defined by the manufacturer in accordance with Article 2 (1) of the MDR [9], an assessment must first be made of how high the probable risk for the user or patient will be in order to be able to carry out a meaningful evaluation and risk assessment of the product. In Annex VIII, the MDR provides the manufacturer with classification rules on the basis of which he must classify his product and divides the medical devices into four risk classes, I, IIa, IIb and III, with Class I representing the class with the lowest risk potential and Class III representing the class with the highest risk potential. [9, 75]

In order to be able to determine in which risk class the product must be classified, it is also necessary to consider, among other things, how long a product is to be used in each case, how it interacts with the body and where, and whether it is an active product with an external energy source or an inactive medical device. For this reason, a well-developed definition of the intended purpose by the manufacturer is essential in advance.

The documentation of the classification under application of the rules laid down in the MDR is carried out mandatorily both in the technical documentation and in the declaration of conformity.

4.4.1 Medical device software

Since software is considered an equivalent medical device under the MDR, the same classification rules apply as for all other medical devices. In this context, the MDR provides some additional guidance relevant to software as a medical device. The most important of these can be found in Annex VIII, Chapter II, 3.3 - 3.5 [9]. Namely, it states:

"*3.3. Software, which drives a device or influences the use of a device, shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right.*

3.4. If the device is not intended to be used solely or principally in a specific part of the body, it shall be considered and classified on the basis of the most critical specified use.

3.5. If several rules, or if, within the same rule, several sub-rules, apply to the same device based on the device's intended purpose, the strictest rule and sub-rule resulting in the higher classification shall apply." [9].

These rules are relevant because software is very often used in combination with medical devices. For example, pure control software is assigned the same class as the medical device, while device-independent software is given its own classification. However, conditions are not always clearly and precisely formulated, which could lead to misunderstandings in interpretation. As an example, consider the following wording: *"[...] Software, which [...] influences the use of a device [...]*[9]", although it is not explained in more detail what exactly is meant by "*influence*". This also clearly shows how important it is to have a differentiated and precise definition of purpose and use. After all, this is what makes classification possible in the first place. Rule 11, which was introduced specifically for software, is also very important:

" Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:

- *death an or an irreversible deterioration of a person's state of health, in which case it is in class III; or*
- *a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.*

Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.

All other software is classified as class I." [9]

Based on these listed requirements, a clear classification of the software should now be possible (see Table 3). However, the definition of some items still leaves questions unanswered. It lacks, as already shown in the example above, in some places clear explanations. For example, the article mentions "*physiological processes*" [9] on the one hand and "*vital physiological parameters*" [9] on the other. But what exactly is meant by the terms, what they include, or whether the two expressions are synonymous, is not explained.

Table 3: Classification of Software as Medical Device according to MDR, Annex VIII (Rule 11)

Intended purpose/use of software	**Possible serious Impact**	**Assigned Class**
Providing information to support decisions for diagnosis or therapeutic purposes	None	**IIa**
	Serious deterioration of a person's state of health or a surgical intervention	**IIb**
	Death or an irreversible deterioration of a person's state of health	**III**
Monitoring of physiological processes	None	**IIa**
Monitoring of vital physiological parameters	Immediate danger to the patient because of nature of variations of monitored parameters	**IIb**
All other	None	**I**

Source: Self developed table based on information from MDR, Annex VIII, Rule 11 [9]

4.4.2 Interim conclusion

The classification rules listed in Annex VIII of the MDR [9] are intended to assist manufacturers in classifying their products. In contrast to the outdated MDD [29], implemented in Germany by the MPG [59], additional sections have been added here that are specifically aimed at the use of software. However, some wording used is insufficiently defined, which could lead to misinterpretations or problems with the correct classification of products. At least this will have to be discussed with the involved bodies, the Notified Bodies or the BfArM, if there is no clear assignment.

A comparison of the requirements for the definition as a medical device with the rules for classification from MDR, Annex VIII [9] shows that a classification of software products in the medical device sector can only be made according to Class I to a limited extent, as was previously the rule with the old MDD [29]. Since the majority of all software in use serves diagnostic or therapeutic purposes in some way, classification in Class IIa at least must be applied to these products, i.e. a corresponding conformity assessment procedure involving auditing bodies will be necessary, including the regulatory consequences linked to it. [75]

4.5 Risk Management – Regulatory Background

4.5.1 General considerations

The main purpose of the MDR [9]is to ensure that medical devices placed on the market offer the highest possible level of safety and perform their intended purpose with an appropriate level of performance. The requirement for this is that the risks that these products may generate for patients, users or third parties are identified, assessed and minimized. The qualification of software as a medical device also means that the manufacturer must prove that the general safety and performance requirements of the MDR are met.

For the fulfillment of these requirements and for the final conformity assessment, the MDR therefore requests suitable measures that can provide this evidence. These are essentially the measures and requirements that were already mentioned in Section 4.2 in the context of the examination of the life cycle of a medical device and will be specified again in this section. Since medical devices are mainly, but not exclusively, technical products, the majority of the assessment of the performance and safety of these products will therefore be carried out by checking whether the technical standards applicable to the respective product class are fulfilled. Most of these standards are now available in a harmonized form. Therefore, it can be assumed that compliance with the safety and performance requirements of the MDR will also be met if the corresponding applicable harmonized standards are met. [74, 75] As already mentioned above, software that has been qualified as a medical device is also subject to proof of conformity with the requirements of the MDR. This is done on the basis of the harmonized standards applicable to software as a medical device. For the risk management of medical devices, the harmonized standard ISO 14971 "*Application of risk management to medical devices*" [57] is the leading standard and therefore plays a central role in the whole process.

In order to understand the very complex process of risk management, however, it is useful to first look at its origins and to take a look at what risk management is based on. As already mentioned in the introductory section, safety and performance are the fundamental requirements for a medical device. The MDR provides an answer to what is meant by this in detail.

Annex I, Chapter I of the MDR [9] contains the basic safety and performance requirements that are generally applied to medical devices. Paragraph 1, which largely corresponds to the text of the old MDD [29] regulation, specifies the individual requirements (Figure 7), which form the base for risk management of the product.

Source: Self-developed graphic based on information from MDR, Annex 1, Chapter I (1) [9] (created with Microsoft® Visio Premium 2010)

Figure 7: Safety and performance requirements for medicinal products according to MDR, Annex I, Chapter I (1)

4.5.2 Elements of Risk Management based on ISO 14971

The MDR explicitly requires in Annex I; Chapter I, 3 and 4 [9] a risk management system that is maintained over the entire life cycle of the product and lists the facts that must be identified, checked and evaluated by the manufacturer and that may ultimately lead to regulatory measures being taken.

ISO 14971 [57] builds on this and describes this required risk management system in detail. The harmonized standard first lists the general requirements for risk management. The first step will be to implement a risk management system that maps the risk management process.

This can be run as an independent process or integrated into an existing QM system, if it has been set up in accordance with ISO 13485 [56], and is therefore compliant with the regulatory requirements. The responsibility for risk management and the availability of a sufficient number of trained employees and sufficient resources lies in the hands of the manufacturer's management. [74]

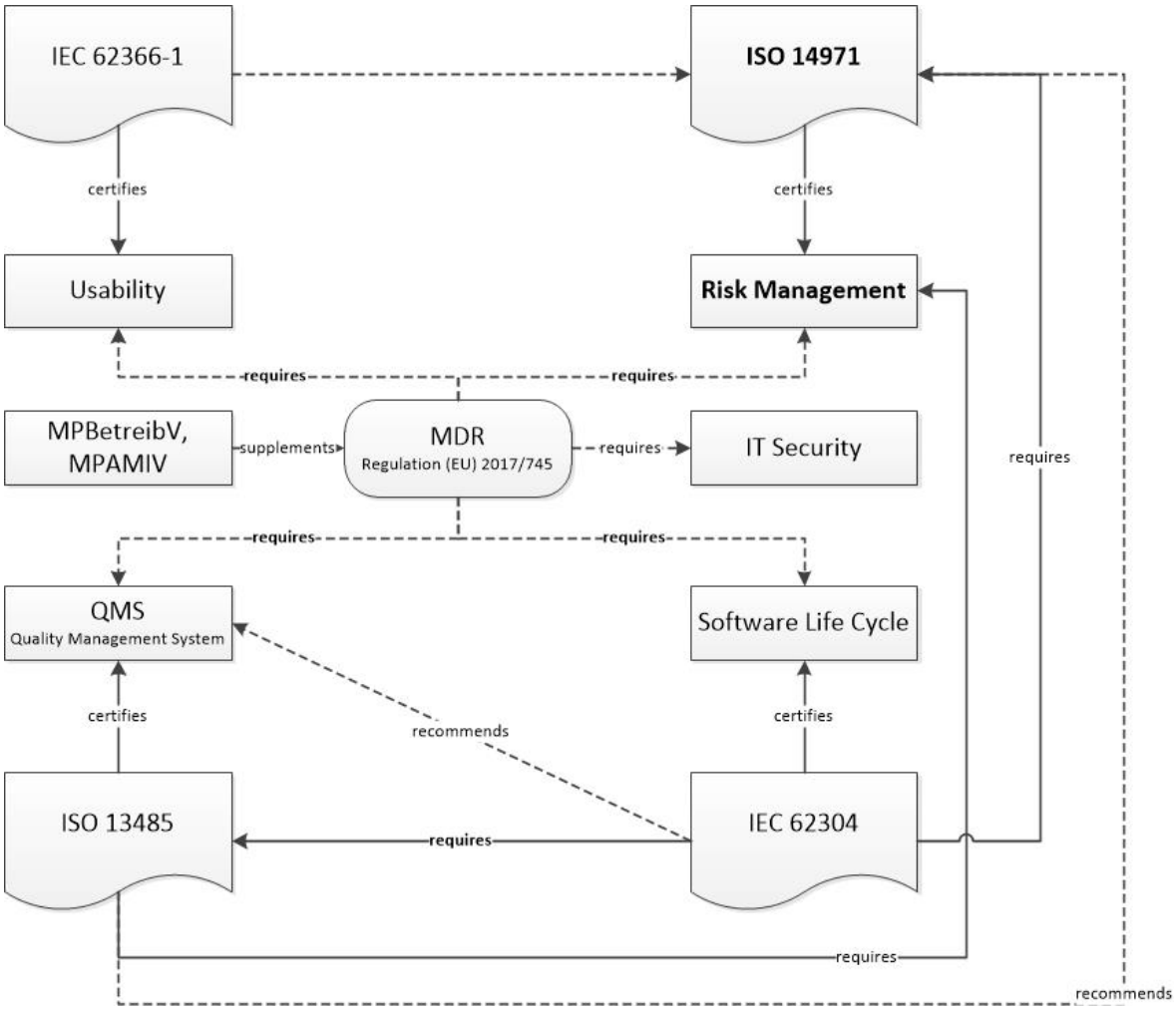
A risk management system must cover the following basic requirements:

- Establishment of a risk management plan
- Risk analysis (identification and estimation of risk)
- Risk assessment
- Risk control
- Risk management file (risk management documentation and reporting)
- Post-market surveillance

4.5.3 Regulatory Landscape for Risk Management of Software as Medical Device

In addition to ISO 14971 [57], which represents the central role and the basis for setting up a risk management system, there are even more software-relevant harmonized standards and factors that have an influence on risk management. These are, e.g. the standards IEC 60601-1-6 [51], which adresses the usability, IEC 62304 [52], which deals with the software lifecycle processes, and IEC 62366-1 [53], which is also involved in the risk management process. If a manufacturer is certified according to ISO 13485 [56], this is considered as proof that he has implemented a QM system, which is mandatory as a basis for a conformity assessment procedure according to MDR, Annex IX [9]. Since ISO 14971 [57] plays a central role, it is referenced by all other relevant standards.

A simplified overview of the regulatory landscape is shown in Figure 8.



Source: Graphic freely adapted from: JOHNER, Christian; HÖLZER-KLÜPFEL, Matthias; WITTORF, Sven. Basiswissen Medizinische Software. 3. Auflage. dpunkt.verlag GmbH, Heidelberg. 2021. p.84 [74] (created with Microsoft® Visio Premium 2010)

Figure 8: Overview of Regulatory Landscape for Risk Management of Software as Medical Device

4.5.4 Interim Conclusion

As the simplified diagram (Figure 7) suggests, risk management involves numerous subprocesses that must make it possible to fulfill the wide range of requirements. Under the generic term "*Safety and Performance Requirements*", Annex I of the MDR [9] provides only a very brief overview of the main requirements, without specifying them in

detail. However, manufacturers are obliged to establish a risk management system, which fulfills the requirement for the highest possible level of safety for patients, users and third parties. The exact structure of the risk management system is also not specified. Only a rough list is given of the most important aspects that will be made obligatory for manufacturers. Since the MDR still leaves many questions unanswered, there will be a need for further regulations. These will generally be harmonized standards, the application of which is referred to in Article 8 of the MDR and also in Annex II 4(b) [9]. Compliance with these standards is accepted as proof of conformity with the MDR. However, these harmonized standards are relatively rigid and are updated only every two to three years, resulting in a new version in each case. Whether this is sufficient in all cases, and whether all cases are covered at all by corresponding standards, in order to meet the MDR requirement for *"[...] software [...] in accordance with the state of the art [...]"* [9] as stated in Annex I, 17.2, can be doubted. The possibility of the European Commission, according to Article 9 of the MDR [9], to issue so-called Common Specifications for these cases, after consultation of the MDCG, which should compensate for this deficit, is a "nice-to-have", but probably ultimately suffers from the fact that firstly, Article 9 does not specify who recognizes this deficiency and sets it in motion for processing, who prepares these Common Specifications at all, and secondly, it is to be expected that the processing of such specifications will become a victim of bureaucracy and will be unnecessarily delayed by formalisms. It is difficult to judge what is "*state of the art*", how long a snapshot of a certain condition can be used as "*state of the art*" and who and with which procedure ensures regular updates. Ultimately, the manufacturer will also have to rely on non-harmonized standards in order to obtain a positive assessment in the context of a conformity procedure with appropriate argumentation and documentation and then to be able to launch the product on the market. [9]

In summary, it can be said that the regulation of medical devices and especially software is a very complex topic due to the enormous range of products and possible combinations. This is also reflected in the number and type of regulatory and normative

documents, some of which are strongly interlinked, refer to each other and whose use and observance represent an enormous challenge for manufacturers, since even the identification of the mandatory standards is relatively difficult (see Figure 8). Developing software according to the "*state of the art*" and also keeping the regulatory documents and standards up to date at all times and making them available to manufacturers in a timely manner could also be problematic. Further consideration of the risk management process will determine which other potential problems may arise.

4.6 Risk Management – Risk Assessment

4.6.1 Definition of risk

The development and manufacture of medical devices automatically leads to the need to deal intensively with the risk management of one's products, as required by the MDR in Annex I, Chapter I (3) [9]. In order to be able to assess the risks of a product, it is important to first understand what a risk actually is. For this purpose, the most important terms of risk management according to ISO 14971 [57] will be briefly introduced here.

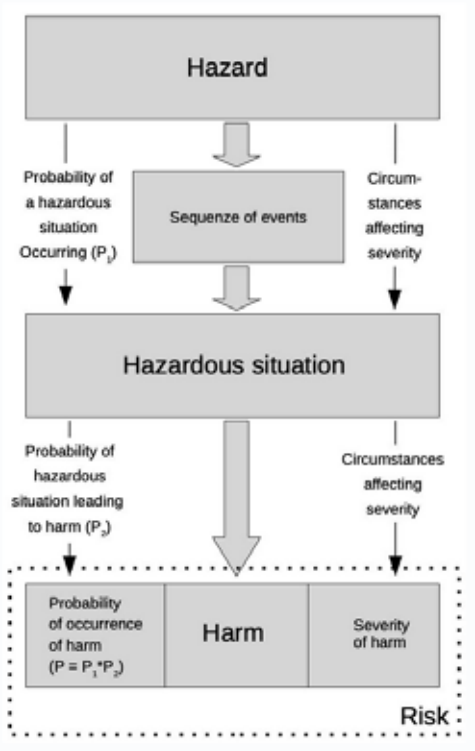
A possible definition of the term "risk" can be found in the MDR in Article 2 (23) [9]. It is described there as a "*[...] combination of the probability of occurrence of harm and the severity of that harm [...]*" [9], whereas ISO 14971 understands "severity" as "the degree of the possible consequences of a hazard" [57]. [74]

The individual terms laid down in the definition of "*risk*" in the MDR are specified in ISO 14971. A summary of the definition can be found in Table 4 and a graphics of the relationships of terms can be found in Figure 9.

Table 4: Definition of terms in the context of risk management

Term	Definition	Source
Risk	Combination of the probability of occurrence of harm and the severity of that harm	MDR
Harm	Physical injury or damage to the health of people or damage to goods or the environment	ISO 14971
Hazard	Potential source of damage	ISO 14971
Hazardous situation	Circumstances in which people, goods or the environment are exposed to one or more hazards	ISO 14971
Safety / security	Being free from risks	ISO 14971

Source: Self developed table based on information from MDR [9] and ISO 14971 [57], and from JOHNER, Christian; HÖLZER-KLÜPFEL, Matthias; WITTORF, Sven. Basiswissen Medizinische Software. 3. Auflage. dpunkt.verlag GmbH, Heidelberg. 2021. [74]



Source: Online: MORGENTHALER, Deborah. Risk Management for Medical Devices under EU MDR and ISO 14971. Decomplix AG, Bern. 19 May 2022. https://decomplix.com/risk-management-medical-devices-eu-mdr-iso-14971/#risk-management-process-under-iso-14971 (accessed 27 Nov 2022) [81]

Figure 9: Definition of relationship of hazard, hazardous situation, harm and risk according to ISO 14971

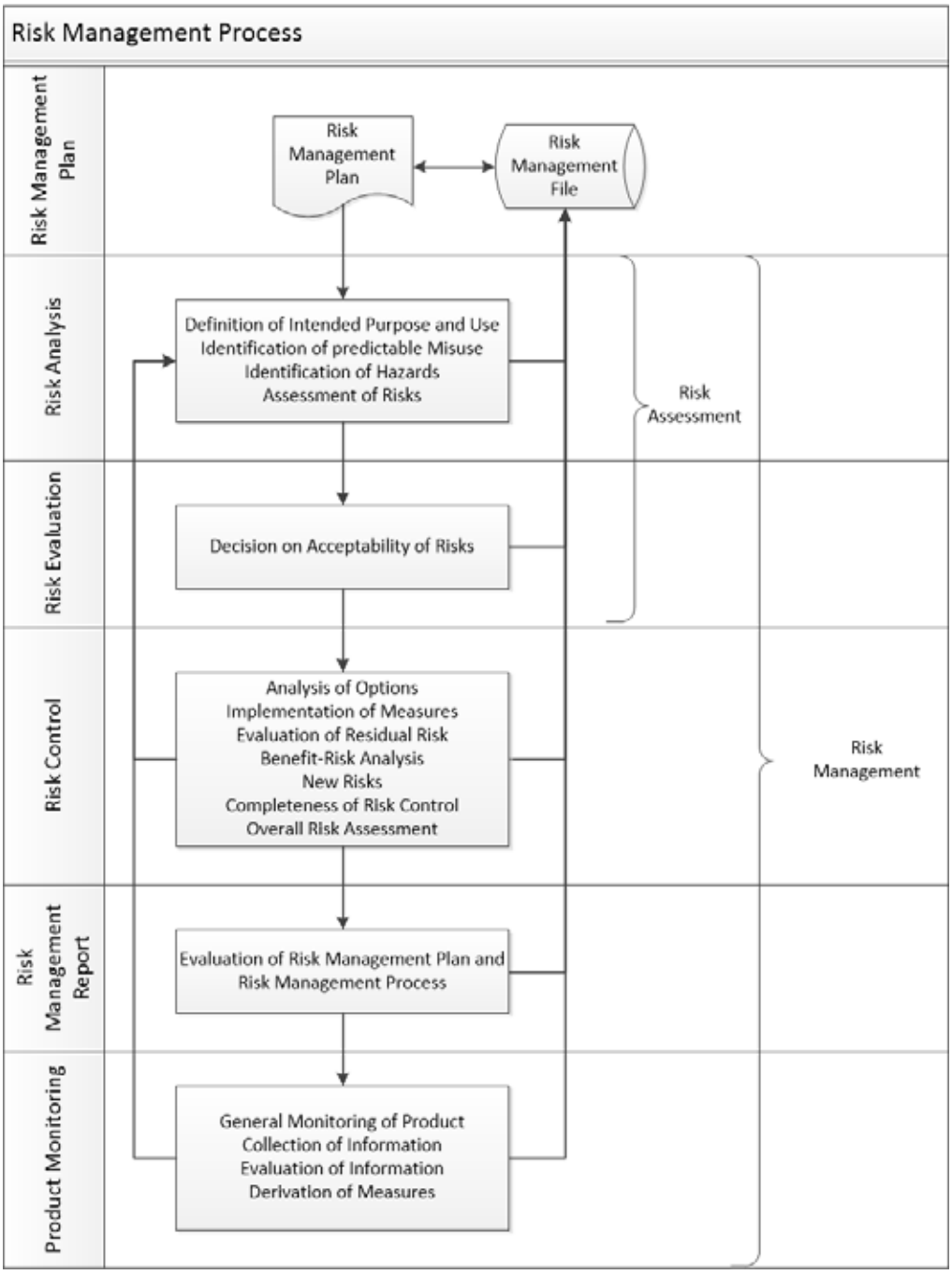
It is noticeable that the absence of risk is covered by two terms. There is a reason for this, because there is a fundamental difference between these terms. Whereas "security" refers to technical safety, such as data security or the failure safety of a device in the case of software, unauthorized access or use, publication of data, whereas the term "safety" primarily refers to operational safety in relation to patients, users or third parties and aims at the protection of life or health, or is to avoid injury. With its requirements, the MDR covers the area of "safety" in the sense of "patient safety", while "security" remains largely a topic in the technical standards. In the further course, aspects in the area of "safety" will be predominantly considered, as this is in the sense of the MDR [9].

4.6.2 Risk Management Process

As it is not possible to manufacture products that do not contain any risks, it is important that possible risks, that may be present are identified, classified and possibly, if this is not already the case, reduced to an acceptable level. Suitable risk management with a defined process in compliance with the regulations is therefore necessary for this. The development of the medical device will take place by means of this process, performed by qualified people with assigned responsibilities and roles, accompanied by a detailed documentation of each of the process step to provide evidence for compliance with the legal framework.

The risk management process is carried out on the basis of ISO 14971 [57]. This standard is not specifically aimed at software, but applies to all medical devices. Section 4.1 of the standard requires the manufacturer of a medical device to set up a risk management process that accompanies the identification, evaluation and, if necessary, elimination of risks during the entire life cycle of the medical device. This includes not only the development phase, in which the product must prove its performance and safety, but also the period after market launch, in which the further development is tracked, any updates or changes made, documented and integrated into a continuous monitoring process. The process itself can be implemented either as a single process or integrated

into an existing quality management system. [74] A simplified overview of the risk management process is shown in Figure 10.



Source: Graphic freely adapted from: JOHNER, Christian; HÖLZER-KLÜPFEL, Matthias; WITTORF, Sven. Basiswissen Medizinische Software. 3. Auflage. dpunkt.verlag GmbH, Heidelberg. 2021. p.101 [74] (created with Microsoft® Visio Premium 2010)

Figure 10: Risk Management Process for Medical Devices according to ISO 14971

4.6.2.1 Risk management planning and documentation

In order to be able to carry out the risk management process, a risk management plan must first be drawn up. Among other things, it sets out in writing all the activities that are necessary for implementation and how they are to be carried out. It also defines responsibilities, identifies any approvals that need to be obtained, and assigns the relevant activities. It also defines the knowledge and skills that employees must have in order to perform the corresponding workflows and activities, and implements a training system in case training still needs to be provided. In addition, all documentation is prepared to demonstrate compliance with regulatory requirements and processes. [74, 75]

In the case of software, which as a medical device must pass through the risk management process, IEC 62304 [52] applies, which describes the special risk management for software. According to this standard, the corresponding product-specific information can instead also be contained in the development plan for the software or in related SOPs (standard operation procedures). [74]

4.6.2.2 Risk analysis and evaluation

For each medical device a risk analysis has to be performed . In order to be able to assess the risk of the medical device in relation to its intended use and to obtain usable information from this assessment that can contribute to the benefit-risk evaluation, the relevant and foreseeable hazards, or the potential sources of harm, must first be identified and the potential risk assessed. For this purpose, the risk must be measurable in some form qualitatively and/or quantitatively. A practical guide is provided by ISO/TR 24971 [58], which contains possible techniques for risk analysis. The risk analysis should in any case cover the following points:

- - The intended use and potentially foreseeable misapplications derived from it.
- - Identification of all safety-related features of the product
- - Identification of hazards and hazardous situations

Annex C of ISO 14971 [57] and Annex A ("Identification of hazards and safety-related characteristics") of ISO/TR 24971 [58] contain a corresponding questionnaire for this purpose, which provides practical guidance for identifying product risks.

Based on this analysis, the risks associated with the hazards are assessed. The risk assessment is based on two main components: the severity of the harm and the probability of the harm occurring. These two components form the two axes of a risk evaluation matrix, which the manufacturer uses in advance, in the risk management plan, to determine the acceptability of potential risk. [75, 80, 81]

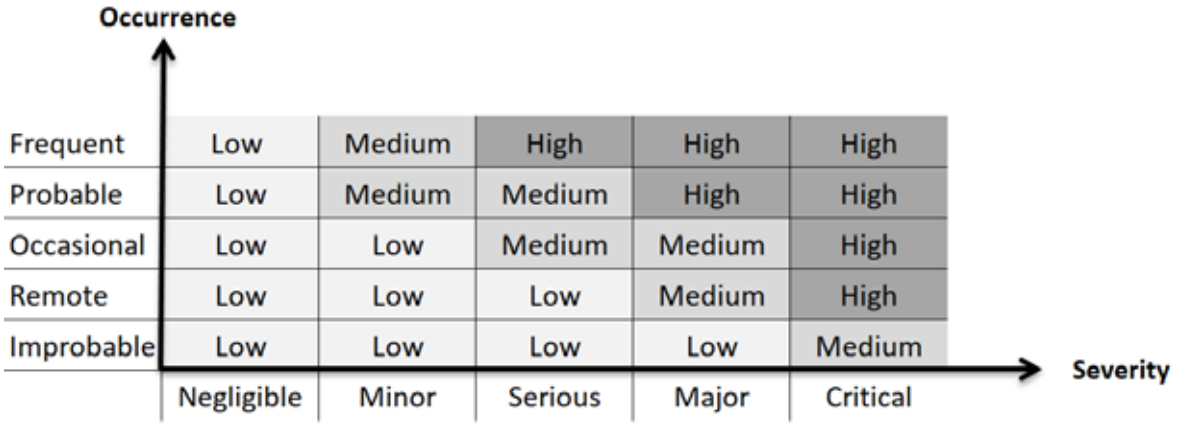
Table 5 shows an example for the criteria according to which a risk evaluation matrix may be set up.

Table 5: Severity and occurrence level in risk evaluation

Severity	Description	Occurence	Description
Critical	Loss of limb; life-threatening injury	**Frequent**	1 in 100
Major	Severe, long-term injury; potential disability	**Probable**	1 in 1000
Serious	Short-term injury or impairment requiring additional medical intervention to correct (e.g reoperation)	**Occasional**	1 in 10000
Minor	Slight customer inconvenience; little to no effect on product performance, non-vital fault	**Remote**	1 in 100000
Negligible	No or negligible risk to patient	**Improbable**	1 in 1000000

Source: Self developed table based on information from ISO 14971 [57]

For risk evaluation, the two parameters are related to each other and the resulting effect is used to define the risk levels (low, medium, high). The measures that must be taken to keep the residual risk of the medical device as low as possible finally depend on the classification of the risk. Figure 11 shows an example of what a typical risk evaluation matrix might look like.



Source: Graphic freely adapted from: HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. [75] (created with Microsoft® Excel 2010); the terms "High, Medium,Low" represent high, medium or low risk.

Figure 11: Example for a Risk Evaluation Matrix for Medical Devices

The assessment of whether a risk is low, medium or high depends on the hazard potential of the device itself, as well as to a large extent on the initially defined intended purpose and use. The combination of the two parameters "severity" and " occurrence" alone can therefore only provide a rough indication of how the determined risk is reflected in the risk-benefit analysis, but cannot be the sole basis for evaluation. The actual evaluation process is far more complex and requires a great deal of technical expertise in order to minimize risks for patients, users and third parties and, which must also not be neglected, the environment. This is because environmental aspects, e.g. due to waste products generated during operation or disposal of the medical device, may also play a role. Consider, for example, medical devices whose raw materials may have to be recycled or otherwise disposed of after they have been discontinued, empty batteries that are accumulating, or, e.g., material medical devices that could potentially be released into the environment. In this area, too, specialized knowledge and assessment by proven experts will be necessary. However, the acceptance of a risk goes hand in hand with the medical benefit of a product, which is why the result of the clinical evaluation, which will be also required in the course of the conformity assessment of a medical device, is a decisive factor in risk management. It is therefore essential, that the Clinical Evaluation Report be

available before the final acceptance assessment. Only in this way can the risk-benefit ratio be determined sufficiently well.

4.6.2.3 Risk assessment of software according to IEC 62304

The risk assessment of software and software components is a special case within medical devices and is embedded in the general risk management process according to ISO 14971 [57]. This process is mapped by IEC 62304 [52], which reflects the additional requirements attached to the existence of software in the field of medical devices (cf. Figure 8). In the case of software, the assessment of hazards also depends largely on the intended purpose and the risk management process is identical to that of conventional medical devices, which is why IEC 62304 [52] also basically refers to ISO 14971 [57]. However, software is not usually a medical device that can cause direct harm to the patient, for example through physical injury, but indirectly due to malfunctions, software errors or improper operation or use. The process of risk analysis and evaluation will therefore have a different character than for "normal" medical devices, but can still contribute to the hazard. [82]

For the development of software that has been declared as a medical device, ISO 14971 [57] must be applied as the basis for risk management, as is the case for all medical devices. In addition, IEC 62304 [52] requires a so-called software development plan to be defined in advance, which defines the activities and tasks to be performed during the development of the product. The manufacturer himself decides on the way in which software development takes place by selecting an appropriate development model. This is not specified by the IEC 62304 standard. [74]

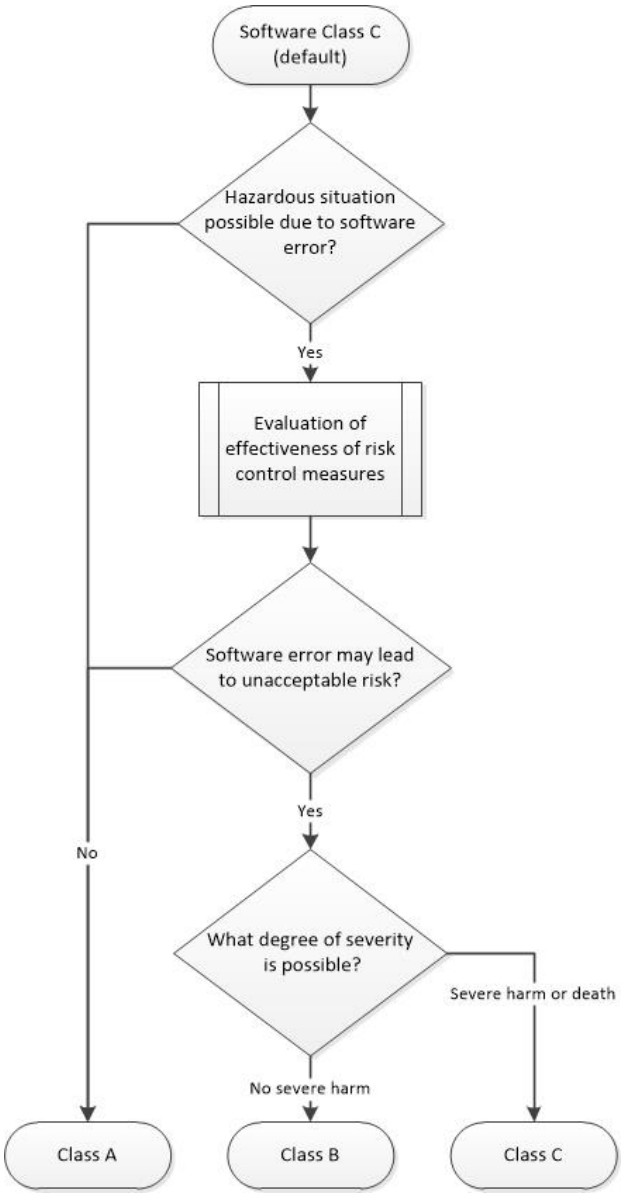
Software development itself is not the subject of this thesis. However, it is based on a differentiated risk management and must be accompanied by it. For the development of the software architecture, the requirements placed on the software must be formulated precisely, comprehensibly and without contradiction in order to be able to ensure subsequent verifiability of the applied test criteria and traceability of the requirements to

their source within the framework of the validation of the software. In the case of standalone software such as apps, this is relatively unproblematic because the software consists of only one component, the app, and the risk analysis only has to be performed for a single module. In the case of combined systems consisting of a "normal" medical device and medical device software, this is much more complex, as the software usually consists of several modules that work together as more or less interrelated units. It is also not necessary for all modules of a software to be declared as a medical device if, for example, they are only used as pure control modules without a medical purpose or are only used to store data without the data being evaluated for diagnostic purposes within the software. These modules are then not subject to regulation and therefore do not require a conformity procedure. [74]

In the course of the risk management of the medical device, the risk management of the associated software is also carried out at the same time. IEC 62304 [52] defines safety classes specifically for software, which represent the hazard levels "Low" (Class A), "Medium" (Class B) and "High" (Class C). This means that the higher the safety class, the more documentation is required for risk assessment and evaluation. In contrast to technical medical devices, the safety class of a software, in the case that an unacceptable risk can be assumed, cannot easily be assessed by the probability of harm occurring, since it is very difficult to determine and evaluate the probabilities of software errors. For this reason, only the extent or severity of the harm can be used to determine the safety class. [74] But risk assessment is not quite that simple. If the greatest possible harm that software can cause is assumed, the highest possible harm classification for the case under consideration is obtained as the basis for the assessment. This can be assumed because software errors do not occur randomly like, for example, a defect or material error in a technical medical device. Rather, they are systemic errors that have already arisen during the development of the software. [75] The risk arising from these errors can be reduced by suitable risk minimization measures, for example by using appropriate hardware to mitigate the risk.

This allows a downgrade in the classification to be achieved, and the documentation effort can also be reduced considerably in part.

A schematic depiction of the determination of safety classes for software according to IEC 62304 is shown in Figure 12.

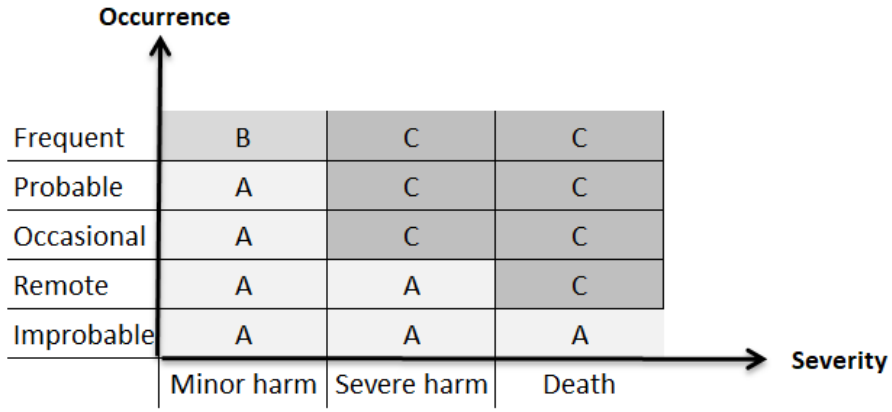


Source: Graphic adapted from: JOHNER, Christian; HÖLZER-KLÜPFEL, Matthias; WITTORF, Sven. Basiswissen Medizinische Software. 3. Auflage. dpunkt.verlag GmbH, Heidelberg. 2021. p.113 [74] (created with Microsoft® Visio Premium 2010)

Figure 12: Determination of the safety class of medical device software according to IEC 62304

It is also common to decompose the software, i.e. divide it into several useful subsystems and to consider each subsystem separately. This makes it possible to identify the most risk-relevant systems. This procedure can lead to the need to assign the various subsystems to different risk classes. What initially appears to be difficult, however, ultimately minimizes and simplifies the evaluation process, since it is not a complex overall system that has to be considered, but rather small subsystems. This also has an impact on the documentation effort during validation, since not so complex processes have to be tested and evaluated. [74]

A matrix which shows the safety classes according to IEC 62304 is displayed in Figure 13.



Source: Graphic freely adapted from: HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. [75] (created with Microsoft® Excel 2010); Classes A, B, and C represent software with the lowest, medium and highest risk

Figure 13: Safety classes of Medical Device Software according to IEC 62304

Some examples of failure in the practical environment of software include:

- The software calculates incorrect values or displays incorrect information, which leads to the user drawing incorrect conclusions regarding findings, diagnoses and therapies, which is equivalent to a hazard for the patient.
- Or the software works correctly, but the user operates it incorrectly, reads incorrectly, or draws incorrect conclusions from the information received.

- IT security (safety) is insufficient, e.g. due to incorrect installation or configuration of the software or unauthorized access. This is not to be seen in the context of data security (security).

4.6.3 Interim Conclusion

Risk management, as a legally required and therefore essential key process in the approval and maintenance of medical devices, is in itself a very complex process that requires a very differentiated risk analysis. Each individual risk identified must be subjected to a detailed risk assessment or benefit-risk analysis, which includes acceptance criteria from standards, quality data, market observations and, very importantly, clinical investigation results, e.g. from the clinical evaluation in the course of the conformity assessment procedure. However, one should be aware that the risk management process already plays a major role during the development of the medical device itself, as the focus is on requirements for the product, compliance with legal requirements and risk minimization for patients and users. The same applies to software that has been classified as a medical device. Most software, as mentioned in previous chapters, is classified as an active device according to MDR, Annex III, Rule 11 [9] as at least Class IIa, but usually often Class IIb, i.e. it is classified as a high-risk device. In addition to the risk assessment of the "technical" medical device, software must therefore also undergo a risk management process right from the development stage. A corresponding procedure is defined in standard IEC 62304 [52], which supplements ISO 14971 [57], the standard to be applied to the risk management of medical devices. The standard also defines safety classes to be applied specifically to software medical devices, which are intended to support a risk assessment of software. However, the analysis and assessment of software risks are much more difficult because, for example, software errors are always systemic errors that do not occur by chance as a result of a technical defect but are embedded in the system from the very beginning. These are usually only mitigated or eliminated by updates in the course of the lifecycle, but must be evaluated from the outset. By the structure of software as modular system, the complexity leads to an enormous documentation effort,

which goes along with that of the software validation. Simplifying procedures such as dividing the software into individual process units makes testing and evaluation easier and reduces the documentation effort considerably.

The danger of risk management is that errors are overlooked or risks are incorrectly assessed during risk analysis. In addition, when changes or updates are made, the risk assessment must follow up and consider the new situation. Also, despite the different standards, the overall product and its users must always be considered, i.e. if changes are made to the software or the technical product, the risk assessment for both must always be updated. [74]

4.7 Risk Management – Risk Control

The result of the risk assessment forms the basis for risk control. Risk acceptance and residual risks are important factors here. The operation of any medical product always involves a certain residual risk. If these risks are already within the acceptance range, they only need to be monitored during the entire life cycle to ensure that they do not leave this range. However, for residual risks that have been classified as unacceptable, measures must be taken to minimize the residual risk as far as possible (see Section 4.7.1).

It must be documented in detail that the planned measures have also been implemented and that they are effective, i.e. evidence must be provided that a sufficient reduction of the previously identified risk takes place and that they do not have a negative impact on already existing risks by increasing them or even that new risks occur which did not exist beforehand.

4.7.1 Control of residual risk through risk minimization measures

According to ISO 14971 [57], risks that still exist must be minimized or reduced as far as possible as part of risk control. To this end, the manufacturer must define measures for risk control, which must be checked and possibly implemented in the specified sequence

as early as possible during product development, since simple implementation is usually still possible at this point.

The following measures are intended for this purpose:

- Highest effectiveness: Safe basic design of the product (integrated or inherent safety). Ensure that the medical device cannot physically create the identified risk.
- Medium effectiveness: protective measures in the medical device itself.
- Lowest effectiveness: user training, operating instructions.

[75, 74]

4.7.2 Re-evaluation of risks

After the implementation of the risk minimization measures, a new risk evaluation must take place. For this purpose, the same acceptance criteria for severity, occurrence, risk levels, and risk acceptability, that were defined in the risk management plan must be reassessed and an evaluation of the acceptability of the residual risk must be performed. The process is the same as that carried out in the original evaluation. The purpose is to evaluate the residual risks to determine whether at least the level of risk has been reduced to an acceptable level or as low as possible. After evaluating the residual risks, it may happen that there are remaining risks that are still outside the defined acceptance criteria and are unacceptable.

4.7.3 Benefit-risk analysis

If it is foreseeable that the residual risk cannot be reduced further, it makes sense to perform a benefit risk analysis. If this is positive, it can be used to justify why even a violation of the acceptance criteria is not an obstacle to continuing with the development of the product. However, this can only be a work-around, because the acceptance of results outside acceptance criteria always requires a well-founded justification and is very likely to lead to far-reaching discussions with the assessment bodies. Therefore, one

should always try to identify suitable measures that can be used to push the residual risk below the critical level.

4.7.4 Emerging risks

If new risks arise during the risk mitigation process, they must undergo the exact same defined evaluation cycle as the initial risks.

4.7.5 Overall risk assessment

The risk control process is finalized with the overall risk assessment. With the help of this process, all remaining residual risks in relation to the entire medical device are considered and evaluated once again. If all risks have been minimized and are in the green zone, the result is documented and the risk control process is completed. If any unacceptable residual risks remain, a final benefit-risk analysis can be performed.

4.7.6 Interim conclusion

Since there is no medical product without risks, the topic of risk control is a very important one. With all products, technical, electronic or material, there is always a residual risk which must always be kept as small as possible in the course of risk minimization methods in order not to achieve any adverse effects for patients or users. For the elimination or reduction of risks, various methods are defined in the standards that are suitable for this purpose. Nevertheless, it cannot be ruled out that the ultimately resulting overall residual risk of the product still exceeds the predefined acceptance criteria. A risk-benefit assessment can then, with appropriate justification, lead to the product being placed on the market if the risk-benefit ratio is positive and a relative safety can be demonstrated by conclusive argumentation.

The greatest danger of errors in risk control lies in the fact that the potentially occurring risks and hazardous events are not fully recorded or the risk control measures are not fully implemented. Furthermore, there is always the risk that the risk minimization measures applied will create additional new risks, which will then also have to go through

the entire risk management process all over again. In addition, other already existing risks could also be changed in their characteristics to the positive or negative, so that a differentiated evaluation of the influence becomes necessary and correspondingly for these risks already planned minimization measures must possibly be adapted.

The risk control of software turns out to be more difficult nevertheless, since probabilities for a damage occurrence for software and software-supported products can be foreseen only with difficulty. Internal errors in software are usually systemic errors whose basis was already laid in the course of the development. They do not appear suddenly, but are already implemented in the system and are identified partly only later, for example with the validation of the software or with the use. These errors can be partially or completely improved or eliminated by later updates or by other safety measures, e.g. by intermediate hardware, e.g. by switching off the system in the event of a malfunction. However, the greatest potential for error lies in the human being himself, who can cause an error in the first place through user errors.

4.8 Risk Management - Risk Management Report

Before the medical device is released to the market, the Risk Management Report must be prepared. It contains the documentation of the review of the risk management process. This is to ensure that the risk management plan has been implemented correctly and that the individual processes have been carried out in accordance with the specifications. If there are any deviations from the risk management plan, these are also documented here. Furthermore, the Risk Management Report includes the result of the overall residual risk evaluation, i.e. the confirmation that the overall residual risk is acceptable. Should the overall residual risk not be able to meet the previously defined criteria, the corresponding benefit-risk evaluation is documented here, which should explain in detail why the product can still be brought to market. In addition, evidence must be provided that more extensive and appropriate measures have been

implemented to collect and verify data from production and the subsequent phases. This is directly linked to post-market surveillance.

4.9 Risk Management - Post market surveillance

In order to increase the safety and performance of medical devices within Europe, the MDR (Articles 83 - 86 and Annex III) [9] commits manufacturers of medical devices to set up a system for monitoring their products placed on the market as part of the mandatory quality management system. This so-called Post-Market Surveillance (PMS) serves to proactively and systematically collect performance and safety data during the entire life cycle of the product in order to evaluate them, to identify new risks if necessary and to initiate corrective or preventive measures in the case of any damage that may occur and, if necessary, also to inform the competent authorities or the Notified Bodies. Serious events, as defined in the MDR [9], which are events that may cause death, serious damage to health or threats to public health, around the marketed product must be reported immediately (Table 6) via the EUDAMED database [83]. This case is called vigilance in the MDR (Art. 87–92) [9] and is regulated separately. [84]

Table 6: Reporting deadlines for serious incidents

Type of incident	Reporting deadline
Serious incident	Immediately, no later than 15 days
Serious incident with death or serious deterioration of the condition of a person	Immediately, no later than 10 days
Serious incident with risk to public health	Immediately, no later than 2 days

Source: Adapted and translated from HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. [75]

In the context of risk management, the PMS is primarily used to identify emerging risks and also to update the risk management file should there be any changes in the evaluated probabilities of harm occurring. [75]

As part of the quality management system, however, the PMS not only provides data related to risk management, but also collects data and information on the use or even incorrect use or clinical data that can be assigned to the usability area, as well as an update of clinical data, which, however, are not part of the consideration in this work.

Post-market surveillance also requires detailed documentation. Which documents are required according to MDR [9] and what they must contain is summarized in Table 7.

Table 7: Documents required for post-market surveillance/vigilance

Document	Content	MDR
Post-market surveillance plan (PMSP)	· Determination of data sources. · Determination of data evaluation process and required measures. · Inclusion of post-market clinical follow-up of justification of non-existence.	Art. 84
Post-market surveillance report (PMSR)	· For Class I devices: · Summary of conclusions from collected data · Description of corrective actions	Art. 85
Periodic safety update report (PSUR) **Class IIa: 2-years period** **Class IIb/III: annually** **Class III+implants: EUDAMED**	· For all device classes (except Class I): · Summary of conclusions from collected data. · Description of corrective actions. · Conclusions from benefit-risk evaluation. · Total sales volume of the product · Estimation of persons treated with the product.	Art. 86

Source: Self developed table based on information from MDR [9], and from HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. [75]

4.10 Usability

The use of medical devices is always associated with risks. On the one hand, these can be risks arising from the products themselves, such as technical safety, defects that occur and can lead to failures or malfunctions that are not the responsibility of the user.

These risks are relatively easy to calculate and can be minimized through adequate risk management, as already described in detail in the sections before. A much greater and incalculable risk originates from the users themselves if the product has not been developed with a sufficient level of usability. This also applies to software that has been qualified as a medical device (see Section 4.1). Incorrect or abusive use can lead to injury or even death of patients, which is why attention must be paid to appropriate usability engineering already during the development process of the product in order to identify and exclude user-related risks in advance.

The MDR clarifies in Annex I, Chapter I,5 [9]what is expected of manufacturers.

"*In eliminating or reducing risks related to use error, the manufacturer shall:*

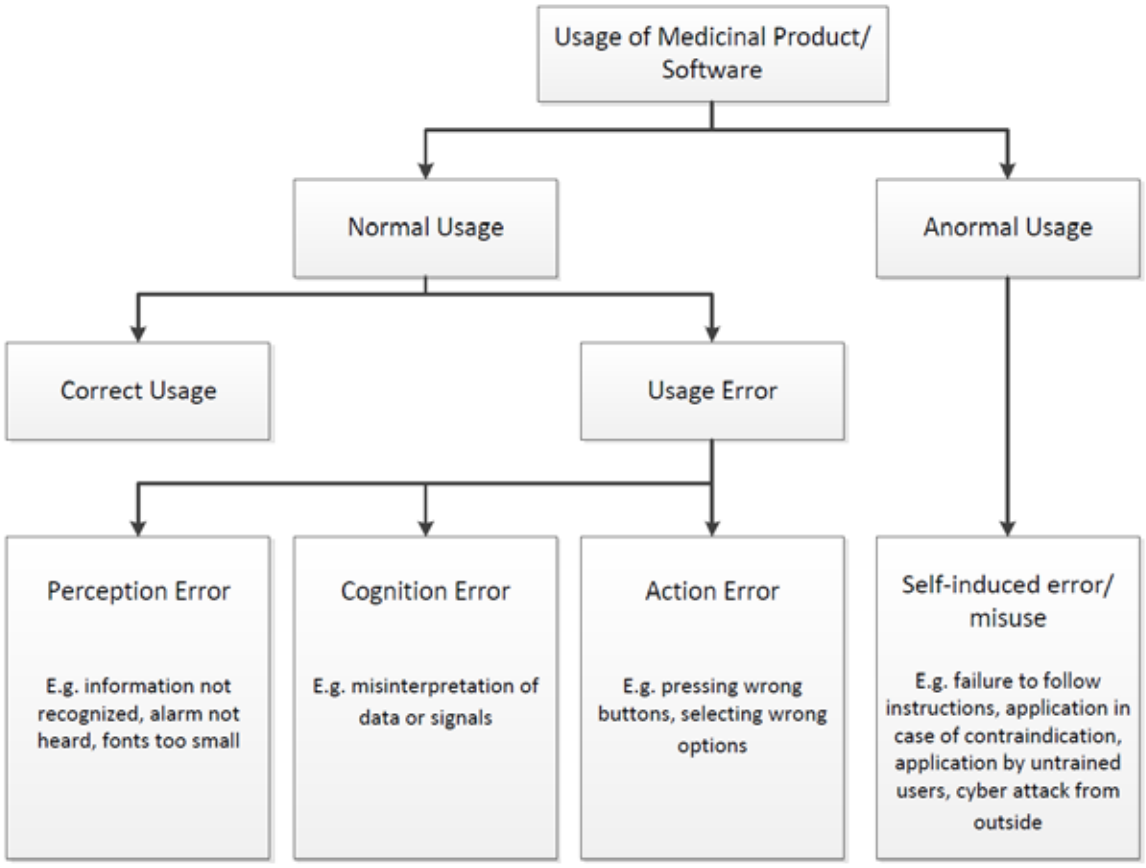
(a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

(b) *give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).*" [9]

Additionally, in MDR Annex I, Chapter III the "*Requirements regarding the information supplied with the device*" [9], which deals with the labeling of the product and the instructions for use that are usually supplied with it, are listed.

The standard IEC 62366-1 [53] implements these requirements and describes the process necessary for the development of a usable product and, with the aid of appropriately formulated requirements, establishes a relationship with the risk management process set out in ISO 14971 [57] (see also Figure 8). The identification of known and foreseeable hazards in the context of usability is mentioned here as a decisive requirement, although according to the definition of usability, user satisfaction and effective and efficient use also play a role. These represent essential characteristics of the product also in terms of marketability, which is why they should not be neglected. [74, 75]

In the development and evaluation of usability, the focus lies on the intended use of the product, with the user interfaces to the users representing the critical elements. Errors can occur either due to incorrect user perception, incorrect interpretation of the data received, or simply due to incorrect or improper handling. The diagram (Figure 14) shows the potential ways a user can use a medical device.



Source: Graphic freely adapted and translated from: HASTENTEUFEL, Mark; RENAUD, Sina. Software als Medizinprodukt - Entwicklung und Zulassung von Software in der Medizintechnik. Springer Vieweg Wiesbaden. 2019. [75] (created with Microsoft® Visio Premium 2010)

Figure 14: Types of Usage of a Medical Device according to IEC 62366-1

This simple graphic already shows that a differentiated development and evaluation process will be necessary to achieve sufficient usability of a product. The basis will be a detailed usage specification, which can also be understood as an extended intended

purpose definition. From this, potential errors can be derived and evaluated on the basis of usage scenarios. Based on the evaluation of the results, a user interface specification can then be created, which then undergoes a final evaluation process. This could also be done, for example, through verification and validation as part of preclinical and clinical evaluation. To get concrete hints on how to develop and implement a usable user interface for software, international standards can also be accessed. An example is the ISO 9241 standard [55], which defines interaction principles and gives design recommendations for interactive systems, e.g., usable graphical interfaces. [75]

To avoid user errors, it is important to provide the user with adequate information material and operating instructions. Training and instruction in the devices and software to be used are also effective means of improving usability for the user.

5 DISCUSSION

5.1 Software as Medical Device - Basis for Discussion

From a legal point of view, a medical purpose assigned by the manufacturer already makes a software a medical device. Within Europe, however, the marketing of medical devices is very strictly regulated by the Medical Device Regulation (EU) 2017/745 [9] and the numerous laws, standards and guidelines attached to it (see Section 3), since very high safety requirements must be applied to products, especially in the medical field, in order to prevent harm to users. The people who generally use this medical software are mostly vulnerable population groups who require special protection due to their physical constitution or existing impairments. Manufacturers of medical devices are therefore confronted with a very high effort to place their product on the market due to the numerous legal requirements that have to be fulfilled. However, this is absolutely necessary, since the use of medical devices is associated with a safety risk that should not be underestimated, and thus there are considerable liability risks for the manufacturer. This bundle of regulations also reveals itself to notified bodies and authorities, on the basis of which monitoring, assessment and approval of the products have to take place.

In the following, a brief summary overview of the problems identified in the course of the work within the approval process of software as a medical device will be given. More detailed explanations of the respective topic problems are contained in the "*Interim Conclusions*" assigned to nearly each chapter of this thesis, at the end of the respective section.

5.2 Problem survey

5.2.1 Problem: Wide-ranging regulatory landscape

Manufacturers and authorities face a confrontation with countless documents (see Section 3). The rather confusing regulatory landscape provides manufacturers and

authorities/notified bodies with very significant challenges. Defining the intended purpose and use of a product as requested from MDR [9] goes along closely with the knowledge of those documents that regulate the current medical device market. It is therefore necessary to obtain a good overview of the current legal situation. From the multitude of laws, guidelines and standards that exist for the various applications, it will be necessary before starting the product development to extract and identify those documents that are relevant and applicable to the desired product and production. This is made more difficult by the fact that there are in part numerous linkages and cross-relationships due to the fact that documents are referencing each other. Another problem is, that the regulatory documents will be continuously updated, supplemented and re-issued, which is very difficult and time-consuming to maintain due to the numerous interconnections and cross-relationships, among other things. During the development of a product, such updates should therefore always be closely monitored in order to ultimately ensure the conformity of the product with the current regulations. Sufficient resources in the the form of specialized personnel who have a good knowledge of the product and the regulatory environment must be kept available for researching the appropriate documents and monitoring the corresponding updates that take place during the life cycle of the product and any new documents that may be added. For more detailed information, see also Section 3.

5.2.2 Problem: Qualification of Software as Medical Device

The entire development and market launch process for medical devices must be carried out in accordance with the requirements of the Medical Device Regulation (EU) 2017/745 [9], which reflects the life cycle of the product. This also applies to software that is qualified as a medical device, because this is also explicitly mentioned in the MDR as a potential medical device. However, qualification as a medical device depends on the defined medical purpose and use on the one hand, but on the other hand it also depends on the function that this software fulfills, whether it is present as stand-alone software, e.g. as an app, as an attachment or as part of a medical device, and which tasks it

performs in this context. This requires a very precise definition of the intended purpose and use, which cannot be derived from the MDR specifications alone. The legally non-binding MDCG 2019-11 "*Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR*" [44] is intended to serve as an assistance for manufacturers as a basis for discussion with Notified Bodies and authorities and to clarify still open points of this partly also quite complex process. The core of the problem lies in the fact that the clear borderlines between healthcare software and medical software or software as a medical device are becoming increasingly vague as a result of the constant supply of new software applications on the market. The gray area in which software finds itself is very distinct. Finally, only the clearly defined purpose and use decides whether a software is marketed as a medical device or not. This also has an influence on the monitoring of safety-relevant aspects, since software not declared as a medical device is not subject to the same high degree of monitoring as is the case with medical devices. For a detailled description, see Section 4.1.2 (Interim Conclusion).

5.2.3 Problem: Development and Life Cycle of Software

The development of medical device software follows the conventional life cycle of a medical device. However, this is only the core area in which the actual software development is integrated. This is supported by numerous standards specifically aimed at software which, if they are harmonized standards, have the character of law. Missing harmonized standards are supported by nationally released standards and regulations. The problem here, as already mentioned at the beginning of this chapter, lies in the cross-referencing and linking of documents, which can be problematic since there is also the risk that statements made in standards and regulatory documents are not always fully compliant. A harmonization of content of standards and the used statements and terms would result in a more clear interpretation of how to develop and maintain software products. For additional information, see Section 4.2.

5.2.4 Problem: Definition of Intended Purpose and Intended Use

Almost the entire development of a medical device and thus also of the software defined as such is based on the definition of the intended purpose and intended use. They are not only the central parameters for the categorization and classification of the medical device and the associated usability considerations, but they also form the basis for the clinical evaluation, which is an essential component in the development process of a product. However, the process of clinical evaluation is not part of this thesis. This important core competence requires that a very detailed definition is established, which must include all parameters and topics laid down in Section 4.3 of this thesis in as clear, comprehensive and complete a form as possible. The problem here lies in the identification of all the components necessary for the detailed definition of the Intended Purpose and Use, which must be completely compiled and documented. For software, it is also necessary to clearly define the type of software and its function in the environment of use. It plays a major role, also in terms of safety, whether software functions as standalone software, as integral software or as an additional component of a technical medical device. For a detailled description, see Section 4.3.3 (Interim Conclusion).

5.2.5 Problem: Classification of software products

Software is classified according to MDR, Annex VIII [9] and the sections included in it, which refer explicitly to it. Compared to the classification rules from the previously valid MDD [29], where most software applications were still assigned to Class I and thus to the lowest class, which from the current point of view was problematic for many areas for reasons of safety, in the course of regulation by the MDR [9], most applications are now assigned at least Class IIa due to their assignment to diagnostic or therapeutic purposes, which places them in the regulatory and testing requirement by Notified Bodies and federal authorities (such as BfArM). As a result, the operation of applications in the medical device sector is now associated with an increased development and monitoring effort for manufacturers, which, however, represents a clear plus in terms of safety.

However, the MDR [9] alone cannot be used to make a precise classification in many cases, as the formulations are in part only vague and insufficiently defined. Here, there is a risk of misinterpretation and, associated with this, of classification in the wrong risk class, which clearly is in opposition to the requirement for minimization of safety risks from MDR, Annex I (1) [9]. Although the MDR in Annex VIII [9] already offers a possibility of approximate classification into a safety class, for many applications, however, due to the constantly developing market, a solution to this conflict seems to be possible at present only through early consultation and discussion with the test bodies involved, the Notified Bodies or the authorities. Here, a much more detailed guidance with case decisions on similar software applications would be helpful for the manufacturer, in order to be able to carry out a simpler and "authority-compliant" classification based on his own considerations. The extent to which data from the EUDAMED database [], the database in which all medical devices operated and on the market in Europe must be registered, could be helpful here, and in what form this data could best be made usable, would have to be investigated in more detail. For more information, see Section 4.4.

5.2.6 Problem: Regulatory Background of Risk Management

Risk management is the basic topic and basis for almost all activities in the medical device sector. As in all medical areas, the focus here is on patient and user safety. As is the case for medical devices in general, the regulatory landscape with regard to risk management is very diverse and closely interlinked. Section 5.2.1 has already referred in detail to the general situation. Exactly the same applies here to the subarea of risk management. The basic requirements to be met in accordance with Annex I, Chapter I of the MDR [9] are supported by numerous guidelines and harmonized standards that map the various sub-processes. Here, too, the laws, regulations, guidelines and standards are closely related and are partly referenced to each other. The most important framework documents are ISO 14971 [57], ISO 13485 [56], IEC 62366-1 [53] and IEC 62304 [52], which is specifically aimed at the life cycle of software. The MDR requirement from Annex I, 17.2, *"[...] software [...] in accordance with the state of the art [...]*" [9] cannot be fulfilled by the

existing and harmonized documents, since the update cycles of the regulatory documents can only keep up with the development in the software sector to an extremely marginal extent and these cannot cover the entire required range. Supplementary standards that are not subject to harmonization can be released as Common Specifications in accordance with Article 9 of the MDR [9]. However, there is no clear assignment of responsibilities as to who should be responsible for identifying deficiencies that arise and triggering the process of creating such specifications. Here, as already stated in Section 4.5.4, there is a danger that necessary extensions of standards will become victims of bureaucratism, which could ultimately be at the expense of patient safety if essential new aspects were left unconsidered. Here, the creation of a structure of clear allocation of responsibility would make sense. Supplementary information on this is provided in Section 4.5.

5.2.7 Problem: Risk assessment

The complexity of software means that the risk assessment for a software product according to MDR Annex I, Chapter I (3) [9] and ISO 14971 [57] must be carried out with considerably more effort than for "normal" medical products, which results in a higher documentation requirement. In addition, software errors are not technical defects, but systemic errors that arise during the development process and are embedded in the system. For this reason, there is a risk that they will be overlooked and thus not included in the risk assessment process in the manner intended. Since software is generally modular, it is a good idea to look at these parts individually during the risk assessment and, if necessary, mitigate or, if possible, eliminate identified errors in an update. All changes made either to the software itself or to a technical medical device automatically lead to a mandatory update of the risk assessment or to a revalidation of the software if the changes are significant. Further details on the Risk Assessment can be found in Section 4.6.

5.2.8 Problem: Risk control and Post-market Surveillance

A safety-relevant issue is always the control of residual risk, since residual risks persist at all times. It is problematic, if the residual risk is on the borderline of the tolerable range, i.e., it can easily go beyond it, or if, for example, risks are not fully identified during the risk assessment or minimizing measures are not sufficiently implemented. However, the minimization of risk is explicitly required by ISO 14971 [57]. Here, the legislator clearly assigns responsibility to the manufacturer. It is very difficult to predict the potential occurrence of damage, since software errors, as already mentioned several times, are of systemic origin, and a differentiated assessment within the framework of a benefit-risk analysis as well as close-meshed monitoring are thus absolutely necessary. In my opinion, however, the legislator has already created a very good basis for action here. The monitoring requested by the MDR in Articles 83 to 86 and Annex III [9], which must be carried out by the manufacturer within the quality management system or as part of a post-market sureillance, respectively together with the EUDAMED database [83], provided by the authorities, offers a suitable means of ensuring the safety of patients and users in the best possible way, as serious events habe to be reported immediately via EUDAMED, so that also the responsible bodies such as Notified Bodies or competent authorities will be informed. This evaluation is based on Section 4.7 to Section 4.9.

5.2.9 Problem: Usability

The highest safety risk in connection with medical devices lies with the people themselves who use the product. A product must be designed and developed by the manufacturer in such a way as to ensure that it can be used by patients or other users easily and with as few errors as possible (MDR, Annex I, Chapter I, 5. [9] This is primarily the responsibility of the manufacturers, especially if the patients themselves are the users. Particular attention must be paid to the user specification. Even a well-considered design of a product can eliminate most sources of error from the outset by supporting the user in the operation of the product through suitable measures, e.g. optimized displays and sound

output, unambiguous data displays, good menu navigation, etc. The manufacturer is responsible for ensuring that the user is familiar with the product. While the manufacturer is responsible for ensuring that the risk of danger is reduced by documenting the product as comprehensibly as possible within the framework of operating instructions and any training that may need to be carried out on the product, which he is obliged to do in accordance with ISO 14971 [57], in my opinion the legislature is also called upon to ensure that usability is also guaranteed for senior citizens and people with other health impairments, so that they can lead a life that is as self-determined as possible and do not have to rely on other people to operate medical devices. As far as can be judged in this context, this topic is also taken up far too rarely in the relevant literature. I see a greater need for action here. Further information is displayed in Section 4.10.

6 CONCLUSION AND OUTLOOK

The use of software in the medical device sector is subject to constant growth [5]. This had to be taken into account with corresponding adjustments in the regulatory area. In general, the regulatory area is currently already well positioned in relation to existing guiding documents. The new Medical Device Regulation (EU) 2017/745 (MDR) [9], which only recently came into force, as a very comprehensive basic document, takes this fact into account, but only provides a fairly rough structure for dealing with medical devices in general and software in particular. In the previously relevant Council Directive 93/42/EEC (MDD) [29], software applications were still treated rather neglectfully and in most cases classified as applications with a low safety class. This changed with the introduction of the MDR [9]. Guidance MDCG 2019-11 [44] was additionally provided for manufacturers as an aid and supporting document for the qualification and classification of software and as a basis for discussion with authorities and notified bodies. However, some of the definitions used in MDCG 2019-11 [44] (see Section 4.1.1.2) differ from those in the MDR [9], which again leads to some room for interpretation that is likely to be confusing rather than

being helpful. Both documents alone are not sufficient for the qualification and classification of software. They must therefore be supported by numerous harmonized standards and guidelines which specifically address the sub-areas to be dealt with. It could be problematic that the documents in some cases are referencing each other, but the contents occasionally contain slightly contradictory statements. Here, improvements would have to be made again, the contents would have to be cross-checked and a common consensus would have to be found. Confusing is not only the number of standards to be used for the individual processes, but also the existing mutual referencing. No satisfactory solution to this problem has yet been found in the short time available. Last but not least, due to the ever faster increase in the number of software developments and the constant further development in the technical sector, there are always small areas that are not covered by the harmonized standards. The MDR [9] explicitly allows the use of non-harmonized standards in order to prove the compliance of a process with the regulatory requirements. Here, it would be appropriate and sensible to identify areas in which important parts are still missing, to supplement the world of standards with these still missing documents, and to harmonize them. Furthermore, it was not possible to identify any regulatory documents which explicitly deal with accessibility of medical devices and medical device software in the context of usability and address the needs and requirements of these highly differentiated and vulnerable user groups. In view of the expected increase in the number of software applications in the next few years [5] and the generally increasing life expectancy of the population [10], a mandatory requirement for accessibility within the framework of a separate standard, at least for the most frequently used applications, would be a step in the right direction in order to guarantee not only patient safety but also the right to a self-determined life for ethical reasons for these patient groups.

7 REFERENCES

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Stolberg, 04.01.2023

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