Diploma Thesis

Additively Manufactured Custom-Made Titanium Implants and related Challenges Under the Regulation (EU) 2017/745

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I declare in lieu of an oath that this thesis was written by me independently according to the recognized principles for scientific papers. All aids used, especially the literature used as a basis, are mentioned, and listed in this thesis. The passages taken verbatim from the sources are marked as such.

The topic of this thesis has not been presented by me in any form as an examination paper to an assessor in Austria or abroad. This work agrees with the work assessed by the assessors.

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Abstract

This diploma thesis addresses additively manufactured custom-made titanium implants with respect to the state of the art of this technology and the related challenges according to the regulation (EU) 2017/745.

It starts with an introduction to the legal framework for medical devices and discusses the Medical Device Regulation (EU) 2017/745 and the Austrian Medical Device Act (MPG 2021). In this regard, custom-made devices, which are a particular type of medical devices, are discussed and their regulatory requirements are presented. The analysis of regulatory requirements for custom-made devices shows that fewer requirements are needed if the medical device is intended to be used for one specific patient. The regulatory demand becomes even more reduced when the custom-made device is manufactured and used only within a health institution.

To provide regulatory knowledge using a hands-on application about manufacturing custom-made devices within a health institution (Center for Medical Physics and Biomedical Engineering, General Hospital of Vienna), an example of an additively manufactured custom-made subperiosteal implant, designed and printed with the Selective Laser Melting is provided. Throughout the process of manufacturing, relevant regulatory documents and standards are indicated and a standard operating procedure is established for future projects of this kind.

Zusammenfassung

Diese Diplomarbeit befasst sich mit additiver Verfertigung von Sonderanfertigungen von Titanimplantaten im Hinblick auf den Stand der Technik dieser Technologie und die damit verbundenen regulatorische Herausforderungen gemäß der Verordnung (EU) 2017/745.

Sie beginnt mit einer Einführung in den rechtlichen Rahmen für Medizinprodukte und diskutiert die Medizinprodukteverordnung (EU) 2017/745 und das österreichische Medizinproduktegesetz (MPG 2021). In diesem Zusammenhang werden Sonderanfertigungen, die eine spezielle Art von Medizinprodukten darstellen, diskutiert und deren regulatorische Anforderungen vorgestellt. Die Betrachtung der regulatorischen Anforderungen für Sonderanfertigungen zeigt, dass weniger Anforderungen erforderlich sind, wenn das Medizinprodukt für einen bestimmten Patienten bestimmt ist. Der regulatorische Aufwand wird noch geringer, wenn das sonderangefertigtes Produkt nur innerhalb einer Gesundheitseinrichtung hergestellt und verwendet wird.

Um regulatorisches Fachwissen anhand einer praktischen Anwendung zur Herstellung von Sonderanfertigungen in einer Gesundheitseinrichtung (Zentrum für Medizinische Physik und Biomedizinische Technik, Allgemeines Krankenhaus Wien) zu vermitteln, wird ein Beispiel für ein additiv hergestelltes, sonderangefertigtes subperiostales Implantat, das mit Selektivem Laserschmelzen entworfen und gedruckt wurde, bereitgestellt. Während des gesamten Herstellungsprozesses wird auf relevante regulatorische Dokumente und Normen hingewiesen und ein standardisiertes Arbeitsverfahren für zukünftige Projekte dieser Art festgelegt.

Content

List of Abbreviations

AFM	Atomic Force Microscopy
AKH	Vienna General Hospital (Allgemeines Krankenhaus)
AM	Additive Manufacturing
ASTM	American Society for Testing and Materials
BASG	Bundesamt für Sicherheit im Gesundheitswesen
CAD	Computer-Aided Design
CE	Chemical Etching
CEN	European Committee for Standardization
CENELEC	European Committee for Electrotechnical Standardization
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CMD	Custom-Made Device
CMDs	Custom-Made Devices
CMPBME	Center for Medical Physics and Biomedical Engineering
CMSI	Custom-Made Subperiosteal Implant
CMSIs	Custom-Made Subperiosteal Implants
CT	Computer Tomography
DfAM	Design for Additive Manufacturing
DFS	Drill-Free Screw
DICOM	Digital Imaging and Communications in Medicine
eIFU	Electronic Instructions For Use
ELI	Extra Low Interstitial
EN	European Standards
ESO	European Standard Organization
ETSI	European Telecommunications Standards Institute
EU	European Union
EUDAMED	European database on medical devices
FDA	Food and Drug Administration (U.S.)
FDM	Fused Deposition Modeling
FEM	Finite Element Method
GSPR	General Safety and Performance Requirements
HIP	Hot isostatic pressing
IFU	Instructions For Use
ISO	International Standard Organization
LCS	Layer Control System
LPBF/M	Laser Powder Bed Fusion of Metals
LPM	Laser Power Monitoring
MDCG	Medical Device Coordination Group

MDD	Medical Device Directive
MDR	Medical Device Regulation
MEDDEV	MEDical DEVices Documents
MPG	Medizinproduktegesetz
MPM	Melt Pool Monitoring
MRI	Magnet Resonance Imaging
NB	Notified Body
PHA	Preliminary Hazard Analysis
PMCF	Post-market Clinical Follow-up
PMS	Post Market Surveillance
PRRC	Person Responsible for Regulatory Compliance
PSUR	Periodic Safety Update Report
QMS	Quality Management System
SB	Sand Blasting
SEM	Scanning Electron Microscopy
SLM	Selevtive Laser Melting
SOP	Standard Operating Procedure
SRN	Single Registration Number
STL	Standard Triangulated Language
STS	Self Trap Screw
TR	Technical Report
UDI	Unique Device Identification
WI	Work Instruction
WKO	Wirtschaftskammer Österreich (Austrian Economic Chamber)

Table 1: Abbreviations

1 Introduction

1.1. General Introduction to the Subject Area

Medical devices, which are appliances that are manufactured for diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of diseases or injuries of human beings [1], are of great significance in public health and thus also in the field of healthcare engineering. In the European Union (EU), medical devices must conform to the Medical Device Regulation (MDR) EU 2017/745 [1]. In addition to the MDR, medical devices in Austria must comply with the Austrian Medical Device Act 2021 (MPG) [2]. Thus, manufacturers of medical devices must fulfill the requirements of the MDR and the MPG to place their medical devices on the Austrian market or put them into service in Austria.

One type of medical device which is mentioned by the MDR is the custom-made device (CMD). Custom-made devices (CMDs) are medical devices that are manufactured for one specific patient. Examples of CMDs are custom-made hand prostheses, knee-ankle foot orthosis, or additively manufactured subperiosteal implants [3]. The MDR and the MPG indicate specific requirements for CMDs, which must be fulfilled, documented, and made available to the Austrian authority (the BASG). Article 5 (5) of the MDR, furthermore, allows the manufacturing and use of medical devices within a health institution. The general hospital of Vienna (Allgemeines Krankenaus, AKH) is such a health institution. Furthermore, the Center for Medical Physics and Biomedical Engineering (CMPBME), which is located at the AKH, has the possibility, given the available production tools, to additively manufacture custom-made implants. However, this possibility is solely discussed theoretically in this thesis since the CMPBME is located in the core process of research and teaching and not patient care. This aspect must be taken into consideration for the realization of in-house production.

With a focus on the CMPBME, this master thesis addresses additively manufactured custom-made titanium implants with respect to the state of the art of this technology and the related challenges according to the MDR and the MPG. In this regard, this diploma thesis analyzes and discusses the MDR's and MPG's regulatory requirements for CMDs manufactured within a health institution such as CMPBME. Subsequently, in the course of this thesis, a CMSI is manufactured with the Selective Laser Melting (SLM) 125 printer (SLM Solutions, Lübeck, Germany) available at the CMPBME as a practical example. In the following, this thesis provides relevant regulatory

documents considering additional applicable standards which describe test procedures or quality and safety characteristics and are necessary to manufacture safe medical devices. This diploma thesis establishes a list of standards for manufacturing a CMSI.

One quality standard for the manufacturing of medical devices is ISO 13485:2016. This harmonized standard requires a documented manufacturing process for medical devices. Therefore, this thesis provides a Standard Operating Procedure (SOP) for the manufacturing of custom-made implants using the SLM 125 printer at the CMPBME. This SOP should serve as a uniform instruction for potential future projects so that the quality is reviewed and relevant documents are created in the same way for every project at the CMPBME. This thesis thus aims to provide the theoretical groundwork for easier traceability, which is required by ISO 13485:2016, and continuous improvement of the manufacturing steps at the CMPBME.

1.2 Research Purpose and Aim of this Diploma Thesis

Nowadays additive manufacturing (AM), in which a raw material is selectively layer-by-layer merged to build an object, is used to manufacture medical devices [4]. In the case of additively manufactured implants, the implants are typically produced by an external vendor and delivered to hospitals for surgery [5]. Thus, the procedure for additive manufacturing of a medical device is usually divided between the external vendor and the hospital. Consequently, the clinical assessment and imaging of the externally manufactured implants are performed in the hospital, while the designing, printing, post-processing, regulatory matters, and characterization including verification, validation, and quality control are performed by the external vendor [6, 7]. The communication between the hospital (including typically a surgeon) and the vendor is of great importance since the medical device must be customized for the patient in the hospital and must be reviewed by all team members from the external vendor and the hospital including the surgeon. This procedure between the external vendor and the hospital requires a processing time of several weeks [5]. For urgent and semi-urgent cases, however, this processing time is too long, for which in-house production could represent a faster alternative. In-house production could also lead to a reduction of the typically high costs for hospitals to purchase additively manufactured medical devices from an external vendor [5].

As performed and discussed in the literature, such as in the work from K. Willemsen et al. [8], and G.E. Daoud et al. [5], a medical device such as an implant, can, however, also be manufactured

within a hospital. In the work from K. Willemsen, two patients were treated with an in-house manufactured custom-made implant. For the first patient, the planning, design, production, and insertion of the implant took six months. After the setup of a Standard Operating Procedure and based on the gained experiences from the first patient, a second patient was treated with a custom-made implant in only six weeks [8]. The work from K. Willemsen thus shows that it is possible to establish a fast manufacturing procedure that covers all the regulatory affairs activities and tests within a hospital after only two runs.

This diploma thesis examines whether a similar manufacturing procedure for medical devices (in-house production) can be performed at the CMPBME at the AKH. The aim of this diploma thesis is thus to determine and analyze all requirements necessary for the in-house production of custom-made medical devices within the CMPBME at the general hospital of Vienna. Based on a hands-on example (custom-made subperiosteal implant), this thesis, furthermore, aims to specify all regulatory requirements established by the MDR and the MPG for custom-made devices additively manufactured within a health institution, such as the CMPBME at the AKH, to define a Standard Operating Procedure, and to determine the additionally applicable standards for potential future AM projects at the CMPBME.

1.3 Structure and Organization of this Diploma Thesis

To determine all regulatory requirements which apply to custom-made devices, a profound knowledge of the European and Austrian regulations on medical devices is required. These legal frameworks are discussed in chapter 2 of this thesis. Chapter 2 begins with an explanation of the MDR and the MPG 2021, with a particular focus on the definition of CDMs according to the MDR and the MPG 2021. In the following, chapter 2 provides an overview of harmonized standards for additively manufactured (3D-printed) devices and the regulatory challenges for custom-made additively manufactured (3D-printed) titanium implants. Chapter 3 of this thesis ("Methods") starts with listing the regulatory requirements for CMDs. Furthermore, regulatory requirements for in-house production are discussed in section 3.2. of this thesis. Subsequently, section 3.3. discusses the AM of a CMSI with the SLM 125 printer at the CMPBME, which provides the practical basis for this thesis. This hands-on example aims to give a better understanding of the procedure and regulatory requirements for manufacturing CMDs within a health institution. Furthermore, an SOP is developed for the manufacturing of CMDs with the SLM 125 printer. Based on the theory of the regulatory requirements and the practical example, chapter 4 of this thesis ("Results") presents

relevant regulatory documents according to the MDR and the MPG 2021 as well as additional applicable standards for the additively manufactured CMSI. section 4.3 of this thesis shows the design and the printed CMSI. Last but not least, section 4.4 of this thesis establishes the SOP with additional comments and explanations. Finally, this diploma thesis discusses the results and gives a conclusion of its findings.

2 Legal Framework for Medical Devices in Austria

2.1. Medical Device Regulation (EU) 2017/745

In the European Union, medical devices have been regulated in a unified framework since the 1990s. Medical devices had since then to comply with the Medical Device Directive (MDD) to be placed on the market [9]. However, due to several serious incidents, the European Union decided to regulate the medical device market more strictly. On April 5th, 2017, the European Commission thus published the new Medical Device Regulation (MDR) 2017/745 [10]. In the new MDR, medical devices are defined as any device which is manufactured for diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of diseases or injuries of human beings [1]. Unlike directives, which provide a legal framework that must be transposed into national law by each EU Member State, regulations are directly applicable across the entire EU [11].

During the MDR's transition period of four years from May 2017 until May 2021, medical devices could be approved according to the MDD and the new MDR [9]. From the 26st of May 2021 on, however, the new MDR applies fully in all EU Member States for the approval of new medical devices [12]. Due to the broad product segment of medical devices, the MDR is very complex and fragmented [13]. Compared to the MDD, the new MDR has 100 articles more and the number of annexes increased from 12 to 17 [10]. The official MDR and other useful documents in this regard

can be found on the official website of EU law (https://eur-lex.europa.eu). A useful mindmap of the MDR with all chapters and their respective content can be seen in figure 1.

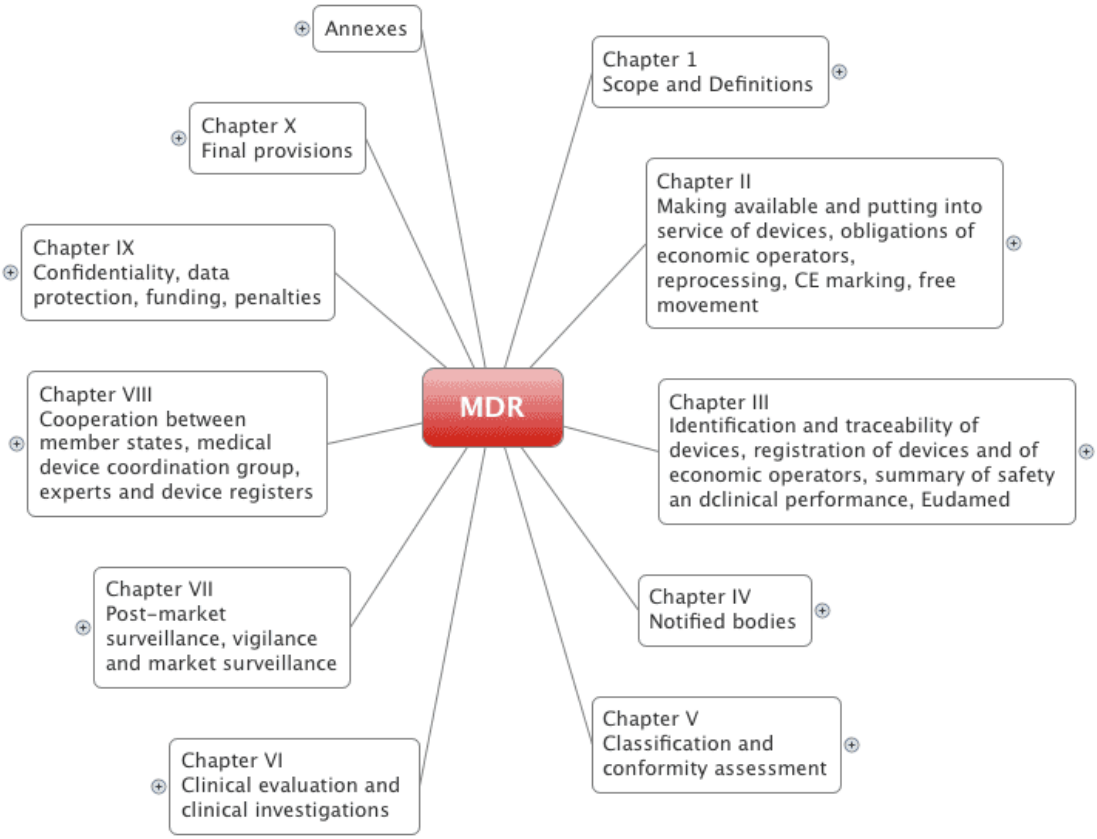

Figure 1: Mind map of the MDR [14].

Despite the direct applicability of the MDR, every EU Member State can adopt additional national laws on medical devices in compliance with the MDR. These national laws can stipulate specific requirements, such as penalties, fees, or distributor registrations [13]. The MDR, nonetheless, remains directly applicable in all EU Member States. Consequently, the Austrian legislators enacted the new Medical Device Act (MPG 2021) in June 2021, which is discussed in the next section [2].

2.2. Austrian Medical Device Act 2021 (MPG 2021)

As discussed in section 2.1, regulations such as the above-mentioned MDR 2017/745 are directly applicable in all EU Member States and do not have to be transposed into Austrian national law according to the European "Treaty on the Functioning of the European Union" [15, 16]. In some cases, however, European legislation requires further measures to be taken by its Member States. In particular, the MDR requires EU Member States to introduce additional measures which deal

with specific, highly technical details of the regulation such as sanctions (art. 113, MDR), levying of fees (art. 111, MDR), and registration (art. 30, MDR) [1, 13, 16]. Consequently, Austrian law should address these measures accordingly [13]. Thus, in June 2021, the Austrian government published the new Medical Device Act (MPG 2021) [2]. The Austrian legal position thus regulates the safety, functionality, and quality of medical devices concerning installation, operation, usage, and maintenance as mentioned in §1 (1) of the MPG [2, 13]. Furthermore, the MPG regulates the manufacturing and utilization of medical devices in health care facilities as well as cleaning, disinfection, sterilization, requirements for clinical investigation and performance studies, the prevention of risks, registration and surveillance, as well as distribution and advertising of medical devices (§1 (1) MPG) [2]. In accordance with the MDR, the MPG, furthermore, designates a national competent authority for medical devices in Austria (§2 (1) and (2) MPG) to implement the MPG and to monitor the market (Market surveillance authority) [2]. This authority is called "Bundesamt für Sicherheit im Gesundheitswesen - BASG" in Austria [2, 13]. Thus, any kind of manufacturing of a 'Medical Device' needs to fulfill the requirements given in the MDR 2017/745 and the MPG 2021, and communication with BASG is thus essential [1, 2].

2.3. Custom-Made Devices according to the Medical Device Regulation (MDR) and the Austrian Medical Device Act 2021 (MPG 2021)

The MDR defines Custom-Made Devices (CMD) as the following:

> "any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs" [1, Art. 2 (3) MDR].

Furthermore, the MDR stipulates the following:

> "However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices;" [1, Art. 2 (3) MDR].

Thus, CMDs are medical devices that are specifically designed and manufactured, intended for the sole use of one specific patient, which should meet the patient's individual conditions and needs.

CMDs are made in accordance with a written prescription of an authorized person and on this person's responsibility [1, 3]. In Austria, this prescription must be given by a person who is authorized by law to prescribe medical aids and appliances (e.g. physician) [17]. According to the last sentence of the MDR's definition of CMDs [1, Art. 2 (3) MDR], a device that is mass-produced and then only adapted to single patient characteristics is not considered a CMD. Furthermore, article 2 MDR stipulates that devices that are mass-produced by industrial manufacturing processes are not CMDs [1]. In this context, the wording "industrial manufacturing processes" is not defined by the MDR. This makes it difficult to understand whether the wording is related to the manufacturer as a company or institution or whether it is related to the process [18]. For such key issues, the Medical Device Coordination Group (MDCG), established by the European Commission, published helpful Guidance regarding the MDR [19]. One of the MDCG's guidelines is the document "Questions and Answers on Custom-Made Devices" (MDCG 2021-3) [3]. In this document, the terms "CMD", "adapted mass-produced device", and "mass-produced by means of industrial manufacturing processes" are discussed and explained by the use of examples [3]. The MDCG 2021-3 also discusses the question, of whether additively manufactured devices are CMDs or not. According to this document and the definition of the CMD, 3D-printed devices which are not mass-produced and contain patient-specific design characteristics that are intended for the sole use of a particular patient are CMDs [3].

Following the path of regulatory challenges for CMDs according to the MDR and MPG, harmonized standards play a significant role and will thus be discussed in the following section [20].

2.4. Harmonized Standards for 3D-Printed Titanium Implants

According to the regulation (EU) No 1025/2012 on European Standardization, the definition of 'standard' is the following [21]:

> A standard is "a technical specification, adopted by a recognised standardisation body, for repeated or continuous application, with which compliance is not compulsory" [21, Art.2 (1) regulation (EU) No 1025/2012].

In this regard, technical specification documents specify requirements and guidelines to describe test procedures or quality and safety characteristics. These technical specification standards are for specific products (e.g. industrial safety helmets), materials (e.g. 3D printable titanium), or

processes and services (e.g. quality management systems for medical devices) [20, 22]. These standards assist organizations to manufacture, develop and provide services or products which are more efficient, effective, and safe [23].

The regulation (EU) No 1025/2012 defines international standards (standards are endorsed by an international body), European standards (standards are endorsed by a European body), and national standards (standards are endorsed by a national body) [21]. Additionally, harmonized standards are defined in article 2 (1) lit. c of regulation (EU) No 1025/2012 [21]. Harmonized standards are developed by a request of the European Commission (also called Mandate) to one of the European Standards Organizations (ESO), namely the CEN (European Committee for Standardization), the CENELEC (European Committee for Electrotechnical Standardization), or the ETSI (European Telecommunications Standards Institute).

As laid out in the above-mentioned definition of standards, the usage of these standards is, however, not mandatory. Thus, an economic operator can choose freely to prove the conformity of his/her device with the requirements of the legislation by using (harmonized) standards or in any other way [20, 21, 24]. However, using harmonized standards for a product or service is a valid and renowned proof that it complies with the requirements of the relevant European legislation and that it reflects the state of the art of the product or service [25, 26]. Thus, it is recommended that the latest edition of the standards is used to reflect the state of the art [26]. These relevant (harmonized) standards can also be used in the field of AM for a manufacturer in order to satisfy the requirements of industrial, commercial, and consumer groups around the world [27]. In section 4.2 of this thesis, the relevant standards for additively manufactured titanium implants are discussed.

2.5. Regulatory Challenges for Custom-Made 3D-printed Titanium Implants

Due to the unique abilities of additive manufacturing (AM), many applications of AM were translated into clinical practice over the last years [18, 28]. This unique development has evolved as an efficient, less expensive, and customized-produced opportunity for medical devices. This also brings along challenges and difficulties regarding the implementation of regulations such as the MDR. These challenges are due to the fact that the material properties of an additively manufactured medical device differ from a device with the same material produced by a conventional manufacturing process [28]. Also, material properties variation can occur within the same AM building process due to 3D printer maintenance and material powder wear [29].

Despite the current challenges, 3D-printed medical devices such as CMDs are regulated by the MDR and do not distinguish between different manufacturing processes [18]. As already mentioned in sections 2.1 and 2.2, CMDs are regulated by the MDR and the MPG in Austria [1, 2]. Thus, all the requirements discussed in section 3.1 of this thesis have to be fulfilled to put CMDs into service or place them on the market.

Furthermore, the MDR specifies requirements and exceptions for devices manufactured and used only within a health institution such as the Vienna General Hospital (Article 5 (5) of MDR) [1]. For CMDs manufactured within a health institution as an in-house device according to article 5 (5) of the MDR, the requirements outlined in section 3.2 of this thesis must be fulfilled [1]. Moreover, the MDCG guidelines [30], the guidelines from International Medical Device Regulators Forum [31], and the guidelines from "Wirtschaftskammer Österreich" (WKO) [17] provide further details on the definition and requirements of CMDs.

A challenging field concerning additively manufactured CMDs is the lack of specific standards (other than the common standards such as ISO 13485). This is often cited as one of the biggest challenges in this context [28]. However, there are currently two organizations that are focused on the development of standards regarding AM. These organizations are the International Organization for Standardization (ISO) and the American Society for Testing and Materials (ASTM) [32]. They developed three series of standards relevant to additively manufactured medical devices. These are the ISO/ASTM 52900 series (from ISO/ASTM 52900 to ISO/ASTM 52950), the ISO 17296, and the ASTM committee F42 [29].

3 Methods

As mentioned already in chapter 1, this diploma thesis addresses additively manufactured custom-made titanium implants concerning the state of the art of this technology and the related challenges according to the MDR. In this regard, a CMSI is printed and the regulatory requirements for such a CMSI are discussed.

This chapter ("Methods") starts with an explanation of the regulatory requirements for the CMSI. These regulatory requirements are essential to put a CMD into service and must be followed. Sections 3.1.1 – 3.1.11 of this thesis discuss every requirement stipulated by the MDR for CMDs. Additionally, section 3.2 analyzes the requirements for CMDs manufactured within a health institution such as the AKH (in-house production). This analysis was performed before the CMSI

was printed in the course of this thesis, as discussed in section 3.3, and should serve as an instruction for the designing and printing of the CMSI at hand and potential future projects at the CMPBME. The information and requirements outlined in sections 3.1 and 3.2 of this thesis shall serve as a guideline for engineers at the CMPBME who want to manufacture a CMD and establish their regulatory documentation.

Chapter "Methods" continues with the experimental basis, which is the CMSI, and discusses every step of the manufacturing process. This manufacturing process includes an introduction to the methods used for manufacturing the CMSI, the design process of the CMSI, the manufacturing process of the CMSI, the post-processing steps, and the characterization methods.

After discussing and breaking down the regulatory requirements, and explaining the AM of the CMSI, this chapter ("Methods") discusses the methods and literature used to establish an SOP for the AM of CMDs (considering the regulatory requirements) at the CMPBME. During the process of regulatory research for the CMSI, 3D printing, and the creation of an SOP, relevant standards are discovered and listed in section 4.2 of this thesis.

For a better understanding of this chapter and thus the methods of this thesis, the central requirements for CMDs additively manufactured within a health institution (in-house production) are presented in figure 2. In its two main pillars, this figure depicts the regulatory requirements from the MDR on the one side and the quality assurance requirements from the literature for the manufacturing of a CMSI (additively manufactured CMD) on the other side. Below these pillars, the figure presents two horizontal bars, which cover the standard operating procedure and the standards that must be taken into consideration throughout the whole process of the manufacturing of the CMSI. The terms listed in the two pillars in figure 2 are further elaborated on in sections 3.1.1 to 3.1.11, 3.3, and 3.4 of this thesis.

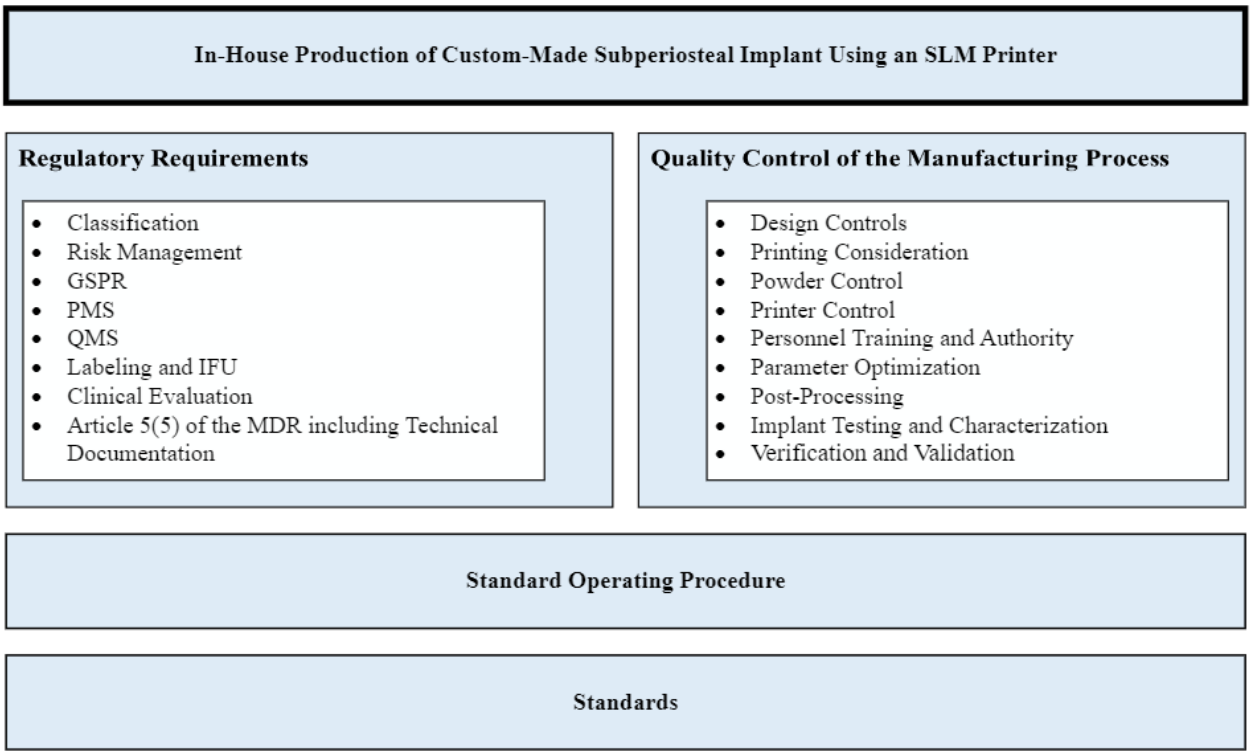

Figure 2: Regulatory requirements and quality assurance during the manufacturing of the CMSI.

3.1. Regulatory Requirements for Custom-Made Devices

In this section, the regulatory requirements for putting a CMD into service according to annex XIII (Procedure for Custom-Made Devices) of the MDR and the MPG 2021 are listed and explained.

3.1.1. Person Responsible for Regulatory Compliance

With the new MDR, a new position named "Person Responsible for Regulatory Compliance" (PRRC) is defined in article 15 [17]. As required in the MDR [1] and described in the MDCG 2019-7 [33], there are two options for a person to become the PRRC. Option one is the possession of a university diploma or certificate in law, medicine, pharmacy, or engineering, awarded by a university in an EU Member State and at least one year of professional experience in the field of regulatory affairs or quality management system for medical devices related to the requirements in the European Union (MDR, Art. 15(1)(a)) [1]. Option two requires four years of professional experience in current regulatory affairs or quality management systems (MDR, Article 15(1)(b))

[1]. For CMD manufacturers, however, the position of PRRC requires only two years of professional experience in the relevant field.

A manufacturer with at least 50 employees and an annual balance sheet total (*Bilanzsumme*) of over 10 million Euros, needs to have the PRRC as an employee within the organization [34]. For other manufacturers with less than 50 employees and an annual balance sheet total of fewer than 10 million Euros (micro and small manufacturers), an external PRRC must be subcontracted [33, 34]. Regardless of whether the PRRC is within the organization or not, it must have a permanent and continuous linkage to the activities of the manufacturer [33]. For manufacturers with more than one PRRC, the responsibilities of each PRRC must be defined and recorded in writing [1].

According to MDR article 15 (3), the PRRC has to ensure that at least the following requirements are met [1]:

1) Before applying the medical device to patients, the conformity of the device with the quality management systems of the organization must be checked. The quality management system for manufacturers of medical devices, however, is established, documented, implemented, maintained, kept up to date, and consistently improved by the manufacturer itself according to article 10(9) of the MDR [1, 33].
2) Another duty of the PRRC (MDR, Article 15 (3) (b)) and the manufacturer (MDR, Article 10 (4)) is to set up the technical documentation for medical devices according to annexes II (Technical Documentation) and III (Technical Documentation on Post-Market Surveillance) of the MDR and to keep it up to date. However, for CMDs, technical documentation is not required according to article 10 (4) of the MDR [1, 17].
   Furthermore, the PRRC and the manufacturer must draw up a declaration of conformity and keep it up to date to place the CE-marked medical devices on the European Union market [35]. However, this is not required for CMDs since the declaration of conformity for CMDs is fulfilled by drawing up a statement according to Annex XIII (1) of the MDR [17].
3) The PRRC has to ensure that the post-market surveillance (PMS) obligations comply with article 10 (10) of MDR [33], while the manufacturer must implement a post-market surveillance obligation and keep it up to date [1]. The PRRC must have a detailed understanding of articles 83 to 86 to fulfill this task.

4) Article 10 (3) lit. d of the MDR refers to articles 87,88,89,90, and 91 of the MDR regarding the reporting obligations. The PRRC is responsible to fulfill these obligations [33]. In this regard, the manufacturer must have a system for recording and reporting incidents and field of safety corrective actions according to article 10 (13) of the MDR. Furthermore, article 10 (3) lit. d of the MDR refers to chapter VII, section 2 of the MDR on vigilance requirements [1].
5) For any systematic investigation involving human subjects to assess the safety or performance of a device (also called an investigational device), the PRRC and the manufacturer must ensure that a statement according to Annex XV (Clinical Investigation), chapter II section 4.1 is given by the natural or legal person responsible for the manufacturing of the investigational device. This signed statement confirms that the investigational device fulfills the general safety and performance requirements and that all the precautions were taken to protect the health and safety of the subject [1, 33, 34].

With regard to liability, according to article 10 (5) of the MDR, the PRRC should not suffer any disadvantages [1]. Articles 10 (6) and 11 (5) of the MDR state that only manufacturers and authorized representatives are liable for defective products as legal entities [34].

These important responsibilities of the PRRC must be fulfilled by CMD manufacturers to meet regulatory requirements and ensure the safety and conformity of medical devices. The specific functions of a PRRC differ, however, from organization to organization [36].

3.1.2. Registration of Custom-Made Devices

Another important requirement according to the MDR for medical devices is registration. In particular, article 108 of the MDR notes that specific device technologies must be registered to collect comparable information. Such registration and the associated databank should lead to an independent evaluation of the long-term safety and performance of medical devices and the traceability of implantable devices [1, 37].

The registration is done using the database “European database on Medical Devices” (EUDAMED) which is provided by the European Commission [38]. Manufacturers are required to submit the device information of all devices they place on the EU market to EUDAMED. Specific medical devices must thus have an assigned Unique Device Identification (UDI) to be placed on

EUDAMED [39]. The UDI is composed of a UDI-Device Identifier for each model of medical device and a UDI-Production Identifier which identifies the unit of device production [1, 40].

However, according to the MDR, CMD manufacturers are exempt from device registration with the UDI in EUDAMED. They are also exempt from the registration of their PRRC in EUDAMED according to the MDCG 2021-3 guidance [3]. Despite that, the manufacturer of class III implantable CMDs must perform a conformity assessment procedure covering Quality Management System (QMS) certification by a notified body. This certification needs to be entered into EUDAMED [3]. Thus, manufacturers of class III CMDs have to be registered in EUDAMED by a notified body (NB) regarding the first QMS certification and they must submit reports to EUDAMED for serious incidents, field safety corrective actions, or any trend reports. After the registration is done, an actor ID will be created automatically by EUDAMED to identify the manufacturer of CMDs. This actor ID is not equivalent to the Single Registration Number (SRN) which is given to manufacturers, authorized representatives, and importers of other medical devices in accordance with article 31 of MDR [41].

Furthermore, the Austrian MPG 2021 has to be considered regarding the registration of medical devices. According to §37 MPG 2021, manufacturers of CMDs have to be registered by their name, address, and type of activity in the Austrian Register for Medical Devices (Österreichisches Register für Medizinprodukte) [2, 13]. Further advice is given on the website of the Austrian Register for Medical Devices which provides a list of actors who must be registered in the Austrian Register for Medical Devices. The website also points out that once EUDAMED is fully available, the registration requirements in the Austrian Register for Medical Devices will be replaced by EUDAMED [42], as stipulated in § 82 (3) MPG 2021 [2, 13].

Additionally, the Austrian Federal Office for Safety in Health Care (BASG) is the national competent authority for medical devices according to §2 of MPG 2021. This competent authority can demand from the manufacturer of CMDs a list of products that have been placed on the market within the scope of MPG [2].

In brief, manufacturers of CMDs have to be registered in EUDAMED. Furthermore, class III implantable CMDs need to be manufactured according to a QMS. This QMS has to be certified by a notified body according to MDR. This certificate and all the reports regarding serious incidents,

field safety corrective actions, or any trend reports must also be registered in EUDAMED. Until EUDAMED is finalized, the registration is done in the Austrian Register for Medical Devices.

3.1.3. Quality Management System

Another relevant requirement for medical device manufacturers, including manufacturers of CMDs, is the establishment, documentation, implementation, and maintenance of a Quality Management System (QMS) according to MDR. This QMS must be continually improved and kept up to date.

According to the QMS standard family ISO 9000, which has global recognition and is applicable to all organizations, a QMS manages interacting processes and resources needed to achieve the desired results and goals. These processes and goals are defined by the organization itself [43]. The QMS allows the top management to optimize their resources and to ensure a safe and effective product or service for their customers [43, 44]. A more specific QMS standard is the harmonized standard ISO 13485, which describes the regulatory purposes regarding QMS for medical devices [45, 46]. Implementing this standard improves the performance and processes within the organization. This, in turn, will lead to cost reduction and more faith from the customer in the product [47].

To establish a QMS within an organization, a hierarchy of documents is used. These documents describe the structure, responsibilities, and content of all processes within the organization and depend on the complexity and size of the organization. These documents are typically quality policies, quality manuals, processes, work instructions, and forms and records [44].

According to MDR article 10 (9) and article 5 (5) (b), manufacturers of medical devices, including CMDs, and manufacturers within health institutions such as the AKH, are required to establish a QMS. In the following table, the QMS requirements for the manufacturer are listed according to MDR article 10 (9) [1]. Furthermore, the corresponding sections of ISO 13485:2016 are listed [10, 17, 45].

MDR article 10 (9) – QMS Requirements:	**The respective clauses in ISO 13485:2016:**
The concept of compliance with required regulations	Section 4.1.1
The determination of the applicable general safety and performance requirements according to annex I.	Section 7.2.1 c)

The responsibilities of the management	Chapter 5
Resource management	Chapter 6
Risk management according to section 3 of annex I	Section 7.1
Clinical evaluation according to article 61 and annex XIV (including post-market clinical follow-up)	Section 7.2.1 c)
Specifications for product realization	Chapter 7
Requirements regarding registration according to article 27 (3) and article 29	Section 7.2.1 c)
A post-market surveillance system according to article 83	Section 8.2.1
Communication with competent authorities, notified bodies, etc.	Section 8.3.3
Procedure for reporting serious incidents and field safety corrective actions	Section 8.2.1
The management of corrective and preventive measures	Sections 8.5.2, 8.5.3
Procedure for monitoring and measuring results, data analysis, and product improvement	Chapter 8

Table 2: The MDR requirements for the QMS in the left column and the ISO 13485:2016 clauses, which respectively fulfill these MDR requirements for the QMS, in the right column.

As can be seen in table 2, the listed requirements according to article 10 (9) MDR can be fulfilled by numerous elements of ISO 13485. Thus, certification of ISO 13485 for the manufacturer of medical devices (such as CMDs) is recommended in order to comply with the regulation [10].

In view of this fact, organizations seeking ISO 13485 certification need to reach out to an accredited body that carries out ISO 13485 certification. In Austria, these accredited bodies can be found on the home page of the Federal Ministry for Digitalization and Business Location (akkreditierung-austria.gv.at) [48]. Furthermore, the received QMS certification for class III implantable CMDs must go through a conformity assessment by a notified body. This information regarding the QMS certification issued by an accredited body for class III implantable CMDs must be entered in EUDAMED by a notified body as mentioned in section 3.1.2 of this thesis [41].

3.1.4. Risk Management System

An important requirement regarding the realization of medical devices is the continuous iterative process of risk management, according to annex I (General Safety and Performance Requirements), chapter I (3) MDR. This requirement is also mentioned in articles 10 (2) and 10 (9) (e) of the MDR,

where the general obligations of manufacturers are discussed. Thus, manufacturers of medical devices (including CMD manufacturers) must establish, document, implement and maintain a system of risk management [1].

Risk management during the lifecycle of medical devices is essential to ensure the quality of the manufactured medical device and conformity with the regulations [10]. Throughout the lifecycle of a medical device, an application such as risk management is for the management policies, practices, and procedures to estimate, evaluate, control, and monitor relevant risks. These risks, which can lead to hazards, should be identified in normal and abnormal conditions. Furthermore, any risks which are judged unacceptable should be reduced to an acceptable level by measures [49].

A specification document, which lists requirements and guidelines with regard to risk management for medical devices, and is harmonized by the European Union, is the standard ISO 14971 [50]. This standard is a suitable aid for the correct application of risk management for medical device manufacturers and offers the procedure for implementing such a risk management system [10]. Additionally, a practical guide that is commonly used for the implementation of ISO 14971 is the ISO/TR 24971 [10, 51]. Fulfilling such risk management standards ensures the identification of device design problems and offers measures to reduce risks as low as possible. Thus, the health and safety of the user and patients are protected. It also demonstrates that the manufacturer provides safe devices [49]. The latest version of ISO 14971:2019 describes a risk management process with the following steps: risk analysis, risk assessment, risk control, residual risk acceptance, and production and post-production information [49]. To understand these steps, it is important to understand the terms harm, hazard, hazardous situation, and risks which are defined in ISO 14971:2019 [50]. The above-mentioned risk management process steps are briefly discussed in the following.

1) Risk Analysis (Section 5, ISO 14971:2019)

In order to analyze the risk concerning the manufactured medical device, the intended use of the device must be defined. For this analysis, the questions in annex A of the standard ISO 24971:2020 can be very useful [10, 51]. These questions can be used to identify characteristics that could affect the safety of the medical device [51]. In the next step, an analysis of all hazards of the medical devices which can lead to harm to the patient or user is done. These hazards are determined under

common as well as under foreseeable maloperation [10]. As a tool, table C.1 in annex C of ISO 14971 can be used. In this table, hazards are divided into energy hazards, biological and chemical hazards, and performance-related hazards [50]. Additionally, different failure analysis methods such as Primary Hazard Analysis (PHA) can be used to evaluate the potential hazards [49]. In the last step of the risk analysis, the risks are assessed by determining the severity associated with the hazards (e.g. negligible, low, serious, etc.) and the likelihood of occurrence of harm to the patient or the user (e.g. unlikely, rare, occasionally, etc.) [10].

2) Risk Evaluation (Section 6, ISO 14971:2019)

In this step, the accepted risks are determined by comparing the severity associated with the hazard and the likelihood of occurrence of harm. In this regard, a risk assessment matrix is used. Thereby, each combination of the two factors is assigned to a specific risk rating by the manufacturer [10]. The manufacturer decides whether a risk is acceptable or not and whether risk reduction is needed [49]. According to the standard, a distinction must be made between acceptable and unacceptable risks in further steps [10, 50]. For acceptable risks, no risk control or risk control measures are needed. Whereas, for unacceptable risks, risk control activities are required [50].

3) Risk Control (Section 7, ISO 14971:2019)

To reduce risks to an acceptable level, manufacturers of medical devices must determine risk control measures. Section 7 of ISO 14971 provides three different options of measures for the manufacturer to reduce risks. The first option is to make the medical device design and the manufacturing process safe [10, 50]. The second option is to take protective measures by preventing the occurrence of a hazardous situation that can lead to harm. The third and last option is providing safety information, instructions, safety signs, and, if appropriate, training for users [50, 51]. Section 7.1.1 ISO 24971 provides further examples for a better understanding of these options of measures [51]. After implementing the mentioned options of measures, the manufacturer has to confirm that the measures are implemented and that the measures in fact reduce the risks. This is done using preliminary products, data analysis, or simulations [10]. In further steps, the manufacturer must evaluate the residual risk according to the abovementioned section “Risk Evaluation” and perform a risk-benefit analysis [10].

4) Residual Risk Evaluation

After the manufacturer identified and evaluated the risks, implemented and verified the measures, and evaluated the residual risks, the overall residual risks must be evaluated concerning the benefits of the intended use of the medical device [10, 50, 51]. A decision must be made as to whether the overall residual risks are acceptable or not. The acceptable and unacceptable residual risks must be estimated and evaluated again [49]. After another risk-benefit analysis, the medical device can nevertheless be placed on the market. The residual risks which are classified as acceptable must be revealed to the public [10, 49].

5) Production and Post-Production Information

Since the process of risk management is a continuous life cycle process, the medical device is being monitored after being placed on the market. In this phase, information is collected and reviewed for relevance to safety. This information can be drawn from general feedback from users, distributors, service personnel, or training personnel [50, 51]. In a further step, this information can be fed back into the first step of the risk management process to analyze, evaluate, and control these risks. In table 7, ISO 24971 provides different sources related to production and post-production information [51].

Medical device manufacturers are obligated to document every step of the risk management process [10]. ISO 14971 specifies requirements as to what must be documented in all process steps [50]. These documents are risk management files or risk management plans, risk analysis records, and risk management reports and are important for the evidence of an established risk management process [10]. As mentioned in the MDCG 2021-3, the risk management process can be applied to groups of devices with the same intended use, materials used, process used, or design, and not for each individual CMD [3].

As can be noticed, the implementation of a risk management system for a manufacturer of medical devices such as CMDs is not only required by the MDR but is also essential for product enhancement and performance safety. Therefore, the establishment, documentation, implementation, and maintenance of risk management are of great importance for manufacturers of medical devices.

3.1.5. Classification

A method, also required by the MDR, to separate medical devices according to the potential risk they are associated with and the vulnerability of the human body is the classification according to annex VIII of the MDR [1, 52]. Depending on the class of a medical device, different requirements are given by the MDR. In this section, the purpose, and the realization of classification according to the rules in annex VIII (Classification Rules) of MDR and the MDCG guidelines are discussed.

National authorities in every EU Member State and notified bodies are responsible for regulatory control of medical devices within the EU. This supervision increases in accordance with the potential of a medical device to cause harm to a patient or user. This, in turn, avoids the unnecessary increase in cost regarding regulations and a delayed market entry [52]. Therefore, medical devices are divided into four risk-based classes (I, IIa, IIb, and III) according to article 51 of MDR [1, 53]. Class I represents the lowest hazard and class III the highest [1, 52]. Depending on the class of a medical device, different requirements are provided by the MDR. Some requirements which depend on the class of a medical device are conformity assessment, clinical evaluation, post-market surveillance, traceability, and instruction for use [53]. The classification of medical devices must be carried out according to the rules in annex VIII of MDR [1]. These rules are divided into four main rules with several sub-rules. The main rules are divided into rules on non-invasive devices, invasive devices, active devices, and special rules, where the strictest rule and sub-rule leading to the highest classification determines the class of that medical device [1]. The intended use and all the device characteristics must be considered during the classification and the manufacturer must consider all rules in order to determine the correct classification for the medical device [53]. The parameters which determine the class a device belongs to are duration, invasiveness, and activeness of the medical device. Considering the rules according to annex VIII of the MDR for the printed CMSI in the context of this thesis, the printed CMSI is a class IIb device [1, 54].

Furthermore, it is essential for the classification to understand the definitions of the terms duration of use, invasive devices, and active devices, according to annex VIII chapter I of MDR. In addition, to the rules in annex VIII, an MDCG document called “Guidance on classification of medical devices” gives relevant and useful examples for each classification rule.

In conclusion, manufacturers of medical devices, regardless of whether manufactured within a health institution and whether this medical device is a CMD, have to classify their medical devices

according to annex VIII of the MDR. Accordingly, different requirements from the MDR are given for that class of medical device and manufacturers have to be aware of those requirements to comply with the law.

3.1.6. General Safety and Performance Requirements – Annex I of the MDR

One of the essential requirements for medical device manufacturers are the General Safety and Performance Requirements (GSPR) from annex I of the MDR [1]. Compliance with this annex is the key to establishing conformity with the MDR [55]. The MPG 2021 states in §5 that it is prohibited to erect, install, put into service, or use medical devices which are not fulfilling the GSPR [2]. The GSPR is divided into 3 main chapters, which are general requirements, requirements regarding design and manufacture, and requirements regarding the information supplied with the device [1]. In the following, the chapters of annex I of the MDR are briefly discussed.

1) Chapter 1 – General requirements

   In this chapter, requirements regarding the design and manufacturing process under normal conditions of use are stated to ensure the safety of the patient and user. Furthermore, this chapter requires the establishment, implementation, documentation, and maintenance of a risk management system [1]. In this regard, the manufacturer must reduce all risks and include necessary control measures to protect the user and patient as described in section 3.1.4 of this thesis [1, 56]. Another requirement in chapter 1 of annex I is the protection of the device during transportation and storage by proper design, manufacturing, and packaging. The medical device must also withstand the stress of normal use during its lifecycle [56].

2) Chapter 2 - Requirements regarding design and manufacture

   In this chapter, detailed requirements regarding the design and manufacture of medical devices are given. Thus, during the design process and manufacturing of medical devices such as CMDs, clauses, and sub-clauses of these requirements which are applicable must be fulfilled to show compliance with MDR. These requirements address the following aspects for all medical devices and provide additional demands for the following types of medical devices [1]:

   - Chemical, physical, and biological properties
   - Infection and microbial contamination

- Devices incorporating medicinal products or biological origins
- Construction of devices and their interaction with the environment
- Devices with diagnostic function, radiation function, or electronic programmable system
- Active devices and implantable active devices
- Protection of patient, a lay person, or user from mechanical risks, thermal risks, and other energies or substances

Detailed information is given in chapter II, clauses (10) to (22) of the MDR [1].

3) Chapter 3 - Requirements concerning the information supplied with the medical device
In the last chapter of annex I, the requirements regarding the information, a manufacturer must supply with a device, are given. Thus, a medical device must be accompanied by information to identify the product and its manufacturer. Furthermore, safety and performance information, which are relevant to the user or other persons must be provided [1, 56]. The latter consists of the label and instruction for use, which have to be available and kept up to date on the manufacturer's website (only if the manufacturer has a website) [1, 55]. Chapter 3 further references article 18 of the MDR. This article provides information that needs to be given to the patient with an implanted device. This is also called an implant card [1]. The MDCG 2019-8 v2 guidance offers examples of implant cards [57].

In practice, these requirements of annex I of the MDR with around 40 clauses and sub-clauses are listed tabularly (GSPR checklist) and it must be checked for each clause whether it is applicable. If a clause is applicable, the manufacturer lists the verification of conformity for this clause. This verification of conformity can either be fulfilled by applying the relevant section or chapter of the MDR or the respective established standard or harmonized standard that fulfills the requirement in the corresponding clause. This GSPR checklist from annex I of the MDR is usually provided by regulatory consulting services which help manufacturers to meet regulatory requirements according to MDR.

3.1.7. Custom-Made Device Procedure According to Annex XIII of the MDR

Manufacturers of medical devices, who want to put a medical device into service or place it on the market, have to demonstrate that the requirements of the MDR are fulfilled [53]. This is done by

the process of conformity assessment and the subsequent declaration of conformity [1]. This assessment depends on the class of that medical device. For higher medical device classes, the involvement of notified bodies is respectively higher [53].

For CMDs, however, the conformity assessment and the resulting declaration of conformity are done by fulfilling clause 1 of annex XIII of the MDR [3]. This is stipulated in article 52 (8) of the MDR, which specifies the conformity assessment procedures for CMDs. Furthermore, CMD manufacturers are required to fulfill all the requirements provided in annex XIII of the MDR before placing the device on the market [1]. This procedure of annex XIII is discussed in the following.

According to annex XIII section 1 of the MDR, CMD manufacturers must issue a statement, which contains the following information [1, 58]:

- The name and address of the manufacturer and all manufacturing sites involved in the production;
- Every data that is needed to identify the medical device in question;
- A statement that the product is intended only for a specific patient. This patient must be identified by her or his name, acronym, or numerical code;
- The name of the person who prescribed the medical device. As mentioned in section 2.3, in Austria, this prescription must be given by an authorized person, who is authorized by law to prescribe medical aids and appliances. The name of the health institution of the authorized person must also be given [17];
- Specific characteristics of the medical device which is prescribed by the authorized person (e.g., physician);
- It must be indicated, which parts of the general safety and performance requirements (according to annex I of MDR and section 3.1.6) have not been met for the prescribed medical device as well as the reason;
- An indication if the prescribed medical device contains the following substances: medicinal substance, human blood, plasma derivative, human tissues or cells, or animal origins.

According to the MDCG 2021-3, CMDs must be accompanied by this statement and this statement must be available to that specific patient or user for whom the respective CMD is intended [3]. This is also required by article 21 (2) of the MDR [1]. Furthermore, this statement from annex XIII

section 1 of MDR must be kept for at least 10 years after the device has been placed on the market. For CMDs that are implantable, the statement must be kept for at least 15 years [17].

In addition to that statement, manufacturers of CMDs must document the design, manufacture, performance, and expected performance according to section 2 of annex XIII of the MDR and keep it available for the BASG. This allows the BASG the assessment of the manufactured CMD with the required regulation in the MDR [1]. The manufacturer must also ensure that the procedure of manufacturing corresponds to section 2 of annex XIII of MDR and, if necessary, take respective measures [59].

Section 5 of annex XIII of the MDR states that manufacturers must review and document experience gained from post-production (as mentioned in section 3.1.4 of this thesis) and from post-market clinical follow-up (as mentioned in section 3.1.9 of this thesis). According to the post-market activities, appropriate corrective action must be applied. Furthermore, any serious incidents or field safety corrective actions must be reported to the BASG according to article 87 (1) of the MDR [1]. Further information regarding the reporting is provided in section 3.1.9 of this thesis.

3.1.8. Clinical Evaluation

Another obligation for medical device manufacturers, including CMD manufacturers, is the implementation of a clinical evaluation, including a Post-market Clinical Follow-up (PMCF) according to article 61 and annex XIV (Clinical Evaluation and Post-Market Clinical Follow-Up) of the MDR. This obligation is required by article 10 of the MDR, where the obligations of manufacturers are discussed [1, 17]. Clinical evaluation is the procedure for collecting, appraising, and analyzing clinical data from the device under question [60]. This clinical data is analyzed to verify whether there is sufficient clinical evidence for the device in question to be in compliance with the general safety and performance requirements (GSPR) according to annex I of the MDR [10, 60, 61]. In this section, the process of clinical evaluation for medical devices according to the MDR is discussed.

Annex XIV of the MDR defines different stages of clinical evaluation. These neat, sequential, and step-by-step (yet also with feedback loops) stages are the clinical evaluation plan (CEP), identification and collection of clinical data, appraisal of clinical data, analysis of clinical data, the clinical evaluation report (CER), and the PMCF [1, 10, 61]. These steps are discussed in the following subsection:

1) Clinical evaluation plan (CEP)

In this step, it is first essential to describe and determine the medical product with its intended purpose. This description must allow the manufacturer to assess the compliance of the medical device with the GSPR in annex I of MDR [61]. Furthermore, the results of risk management with regard to residual risks and possible undesirable side effects must be determined [10]. According to this information, the manufacturer specifies the CEP with the below-listed content as defined in annex XIV, part A, section (1) [1]. For a better understanding of the structure of CEP, guidelines such as the MEDDEV 2.7/1 revision4 [60], MDCG 2020-5 [62], and MDCG 2020-6 [63] provide relevant examples.

In the following, the content of the CEP is discussed:

- Determination of GSPR with the help of clinical data [10]. The manufacturer should analyze the information in GSPR to determine if further data is required to support the clinical evidence of the medical device [63].
- Determination of the intended purpose and the target group of the medical device. Annex II, subsection 1.1 of the MDR and the MEDDEV 2.7/1 guidance list additional information regarding the device description [1, 60, 63].
- For the evaluation planning, it is relevant to describe the positive impacts of a device on the patient. The nature, extent, probability, and duration of the intended clinical benefit must be considered. In this section, it is also important to define specific clinical output parameters to identify, assess, and analyze the clinical data [60].
- In this section, all the qualitative and quantitative aspects of clinical safety and performance must be specified considering also the residual risks and side effects [1, 63]. The guidance MEDDEV 2.7/1 gives some examples of scientific validity to prove appropriate clinical safety and performance [60].
- The clinical benefits of the patient must be specified considering the defined clinical output parameters. Based on the state of the art, specified parameters must be used to determine the acceptability of the benefit-risk ratio. It must be stated, how all benefit-risk components are to be handled [1].
- A clinical development plan must be provided with all the phases of the study including the PMCF [1].

Available research databases can be used to search for measurable, patient-relevant parameters and clinical data on clinical safety and performance [10].

2) Identification and collection of clinical data

According to the MDR, "clinical data" is information concerning safety or performance from the use of a medical device. This data can be from clinical investigations, reports from scientific literature, and information coming from PMCF [1]. During this phase of clinical evaluation, all the available clinical data generated by the manufacturer during pre-market and post-market phases or clinical data for equivalent devices must be collected [63]. The literature research is done according to the state of the art of the related medical field and according to the medical devices themselves [10]. The MEDDEV 2.7/1 guidance, gives further information regarding the systematic literature review [60]. For medical devices which are technically, biologically, and clinically equivalent, the same clinical data can be used for the clinical evidence. The MEDDEV 2.7/1 guidance provides requirements that have to be fulfilled for medical devices to be equivalent [10, 60].

3) Appraisal of clinical data

The identified and collected clinical data is appraised in this section of the clinical evaluation. The data is evaluated to see whether the clinical data is relevant for the effectiveness, clinical safety, clinical benefits, clinical performance, clinically detectable residual risks, and the desirable side effects of the medical device in the intended clinical application areas [10]. Furthermore, the medical state-of-the-art in the field of application must be compared and checked for acceptability with the benefit-risk ratio [10]. Additionally, methodological quality assessment tools can be used to assess published clinical data [63].

4) Analysis of clinical data

The appraised and weighted clinical data must be analyzed in a structured way in this section of the clinical evaluation. This analysis is done to verify whether and to what extent the medical device is complying with the GSPR. In this regard, the GSPR and the acceptability of the benefit-risk ratio are compared to the state of the art [10]. This analysis is done using reliable literature review methods, comprehensive results analysis, gap

analysis, and determining all needs to perform a PMCF. The guidelines MDCG 2020_6 and MEDDEV 2.7/1 give practical guidance for clinical data analysis [60, 63].

5) Clinical Evaluation Report (CER)

The next step of the clinical evaluation is the preparation of the Clinical Evaluation Report (CER) [10]. The CER content and its amount of information depend on the device or technology [60]. CER contains descriptions of clinical evaluation and its processes with working steps and results. This report represents the clinical evidence for the medical device under question [10]. Where it is necessary, the CER should refer to other relevant documents that support the CER document. Furthermore, in the CER, it should be clear which statements are supported by which data and which statements are the opinion of the evaluator. Additionally, references to other data in literature must be included in the CER document [60]. The creation of a CER is also required by the MDR in article 61 and section 4 of annex XIV [1]. Further details on the content and the structure of the CER are described in MEDDEV 2.7/1 [10, 60, 63].

6) Post-Market Clinical Follow-Up (PMCF)

Following the path of clinical evaluation, the process of Post-Market Clinical Follow-Up (PMCF) is an essential part, which is described in annex XIV, part B of MDR [1]. PMCF is part of post-market surveillance (PMS) [64]. The latter is described in section 3.1.9. of this thesis. PMCF is a systematic and continuous process that collects clinical data after the medical device is placed on the market or is put into service [10, 64]. The collected clinical data from PMCF is used to prove the clinical performance and safety, and efficacy with clinical evidence during the lifetime of that medical device [10]. This data can also be used to determine the acceptability of identified risks and side effects. This allows either the acceptability of the benefit-risk ratio or possible misuse of the medical device [64]. New results and findings from PMCF must be included in an update of the clinical evaluation [10]. According to the MDR, the PMCF is a plan-based process, and the collected clinical data from that plan must be presented in the PMCF evaluation report [1, 10]. Annex XIV of MDR and the MDCG 2020-7 specify requirements regarding the content of the PMCF plan. In the MDCG 2020-7, a helpful template is provided [1, 65]. Consequently, a PMCF plan must consist of the following: general and specific methods and procedures, justification for the adequacy of these methods and procedures, references to other relevant

documents, specific aims, evaluation of similar devices, and a detailed schedule [64]. Each finding and result from the PMCF plan must be documented in the PMCF evaluation report. This report must be taken into account when updating the clinical evaluation, the risk management documents, and the post-market surveillance plan. The MDCG 2020-8 guidance provides a PMCF report template for manufacturers to comply with the requirements in the MDR [66].

Overall, clinical evaluation is a requirement from the MDR which is mandatory for medical device manufacturers. The clinical evaluation is done to prove that the medical device is working according to the intended use and that the safety and performance requirements are fulfilled. Furthermore, through the process of clinical evaluation, the acceptance of the risk-benefit ratio and the absence of undesirable side effects are shown [59]. The MDR requirement regarding clinical evaluation also applies to CMDs [3, 17, 59]. However, according to the MDCG 2021-3, manufacturers of CMDs can apply these requirements to groups of products with the same intended use, material, process, design, or other relevant factors characterizing the CMD, instead of to each individual CMD [3].

3.1.9. Post Market Surveillance and Vigilance

Another requirement for medical device manufacturers (including CMD manufacturers) is the implementation of a Post-Market Surveillance (PMS) system. This requirement is stipulated in article 10 paragraphs 10 and 9 lit. i of the MDR, which lists the obligations of the manufacturer. Both of these paragraphs (articles 10 (10) and 10 (9) lit. i) require a PMS in accordance with chapter VII, section 1, article 83 of the MDR [1]. Furthermore, manufacturers must report any serious incident and field safety corrective action in respect of devices made available on the EU market to relevant competent authorities such as the BASG in Austria [1, 17].

The PMCF explained in the previous section is a subset of PMS. While the procedure of PMCF gathers clinical data and updates the clinical evaluation, the data gathered in PMS is used to decide on measures needed to ensure the safety of the patient and user. In this regard information on behalf of risks during the practical use of the product, performance of the product, product defects, and risk-benefit assessment are gathered during the PMS [67]. The process of PMS is essential since certain risks will reveal themselves only after usage on a daily basis [67]. Thus, the manufacturer

is required to plan, establish, document, implement, maintain and update a PMS according to article 83 of the MDR [1, 17].

In this regard, a PMS plan (article 84 of MDR) must be established to systematically gather, record, and analyze information on the quality, performance, and safety of the device throughout its lifetime [1]. The gathered information must be used to identify risk, efficiency, product defects, and undetected safety issues, and to update the benefit-risk assessment. In this regard, corrective measures, such as a recall of the device, can be taken [67].

For class I medical devices the procedure of PMS according to the PMS plan, the results, and the corrective measures must be gathered in a PMS report according to article 85 of the MDR [1, 17]. This report for class I devices has to be updated if necessary [17]. For class IIa, IIb, and III devices, a Periodic Safety Update Report (PSUR) according to article 86 of the MDR must be prepared. For class IIb and III devices, this report is updated at least annually. For class IIa devices, the report must be updated if necessary, but at least every two years [17, 68]. Besides, an MDCG on PMS and PSUR is named on the website of the European Commission for further guidance. However, this MDCG is still in the drafting process and has not been finalized yet [30].

The process of PMS is not only a requirement stipulated by the MDR but also a part of ISO 13485, which is the standard for quality management of medical devices, and ISO 14971, which is a risk management system for medical devices [45, 50]. Both, the PMS report for class I devices and the PSUR for the other three classes must be part of the document according to annex XIII, section 2 of the MDR (documents for the BASG in Austria) [3]. The procedure of PMS can be applied to groups of devices for risk management and the clinical evaluation explained in section 3.1.8 [3].

Another relevant point concerning post-market activities is chapter VII, section 2 of the MDR on vigilance [1, 17]. In this regard, manufacturers must record and evaluate incoming complaints. The evaluation is done to see if the respective incidents can be traced back to a malfunction of the medical device and whether the result is serious for the person concerned [10]. A serious incident is defined as any incident that directly or indirectly has led, could have led, or could lead to death, serious worsening of the health of a person concerned, or a serious public health threat [1]. Any serious incident and any field safety corrective action must be reported to the competent authorities (the BASG in Austria). In particular, serious incidents must be reported immediately. “Immediately” means without unjustifiable delay [10]. The reporting deadlines depend on the

severity of the incident and should not be longer than 15 days after the serious incident happened [10, 17]. For the reporting of serious incidents of CMDs of class III, the EUDAMED database must be used as mentioned in section 3.1.2 of this thesis [17]. As with the PMS and PSUR, an MDCG is in the drafting process to provide a better insight into the concept of vigilance [30].

In brief, every manufacturer of CMDs within the EU must implement a PMS procedure to ensure that the reclamation during application from the user or patient is documented and analyzed and that preventive and corrective actions are performed. In this regard, the manufacturer must report every serious incident and all corrective actions taken. These requirements are established in chapter VII of the MDR [1].

3.1.10. Labeling

Manufacturers of medical devices have to identify the medical device and its manufacturer and communicate all the relevant information on safety, usage, and performance. This is done by labeling, which is described in annex I, chapter III of the MDR [1, 69]. This section of the MDR specifies details on what information the manufacturer must include with their product to ensure that it can be identified clearly and that all relevant information about the safety and performance of the device is made available to users and patients. In this regard, the term labeling includes the label, the instruction for use, and all information on the identification, technical description, and intended use of the medical device [10]. In this section, the requirements regarding the label for medical devices according to the MDR are discussed.

The term label is defined as “the written, printed or graphic information appearing either on the device itself or on the packaging of each unit or the packaging of multiple devices” [1, Art. (2) (13)]. This information on the device shall identify the medical device and the manufacturer. Furthermore, the label provides information regarding the safety and performance of the device for the user and patient. The content, location, type of medium, and legibility of the label depend on the type of medical device [69]. This information can either be on the device or the packaging [10, 17]. Annex I, chapter III, article 23.2, specifies the content of the label of medical devices.

In particular, the content of the label for CMDs must be the following [1]:

- The label ‘custom-made device’;
- The name of the device;
- For packaged products, information on what the product is;

- The name and address of the manufacturer;
- An indication if a human or animal origin tissue is used;
- An indication if substances listed in annex VI of the European regulation 1272/2008 [70] are used according to section 10.4.5, chapter III, annex I of the MDR [1];
- A clear identification, such as serial number or lot number;
- The date until which the product can be used safely or the date of manufacture;
- An indication of any specific requirements regarding the storage or handling of the device;
- If applicable, an indication that the device is supplied sterile with its sterile state and the sterilization method;
- Any warnings which refer to the instruction for use;
- An indication for single use, if applicable;
- The label 'medical device' for medical devices;
- An indication for devices that are introduced into a human body and are absorbed by the human body;
- For implantable devices, the serial number or lot number;

Regarding the labeling of medical devices, the requirements of chapter 7 (ME EQUIPMENT identification, marking, and documents) of the standard EN 60601-1:2014 can also be used [71]. According to the MDCG 2021-3 guidance, CMDs are exempt from labeling and do not need CE or UDI labeling [3]. However, the WKO guidance on CMDs recommends labeling according to annex I of the MDR to communicate the relevant information to patients or users of that device [17].

3.1.11. Instructions For Use

Another information that needs to be provided with the medical device is the Instruction For Use (IFU) to ensure the identification of the product and its information regarding safety and performance [10]. Since an incomplete and inaccurate IFU can lead to harm to the patient and user the IFU is specifically regulated by the MDR [72].

The MDR defines the IFU as information that is provided by the manufacturer to inform the user about the intended use, proper use, and any precautions for the device. This information must be provided with any medical device but can be omitted for class I and IIa devices if these devices can be used safely without any instructions [1].

Furthermore, the IFU can be provided electronically (eIFU) if certain conditions are applicable in accordance with regulation (EU) 2021/2226 [73]. According to this regulation, specific devices such as implantable devices and fix-installed devices must fulfill several requirements for the manufacturer to be allowed to provide an eIFU. These requirements are for example that the device is used only by professionals, risk analysis has been carried out, the IFU can be made available on paper within seven days, etc. [73, 74].

Another important point regarding the creation of an IFU is the language. Article 10 (11) of the MDR requires the IFU to be provided in one or more official EU languages depending on the Member State in which the device is made available [1, 72]. Furthermore, §7 of the MPG requires information that is given to the patient or user to be in German. This paragraph of the MPG stipulates, however, that an IFU of medical devices which are used by professionals only can be written in English [2]. For the content of the IFU the particulars in annex I, chapter III, section 23.4 of the MDR can be used [1]. Furthermore, the guidance on CMDs from the WKO can be used for the preparation of an IFU [17].

In conclusion, CMD manufacturers in Austria must create an IFU. If the device and the intended purpose fulfill the requirements of regulation 2021/2226, the manufacturer of CMDs can prepare the IFU electronically (eIFU). Annex I, chapter III, section 23.4 of the MDR states the requirements for the content of IFU.

3.2. Regulatory Requirements for Custom-Made Devices manufactured and used within Health Institutions (Article 5 (5) MDR)

In section 3.1 of this thesis, the general requirements regarding the manufacturing of CMDs that shall be placed on the market or put into service were discussed. These devices which are manufactured by a manufacturer of medical devices can be placed everywhere in the EU market. Article 5 (5) of the MDR, further describes the option of health institutions to manufacture, modify and use medical devices within their institution [1]. This section takes a closer look at article 5 (5) of the MDR and describes the requirements which must be fulfilled for a health institution to manufacture medical devices such as CMDs and to put them into service.

To begin with, it is important to understand the definition of "putting into service". In article 2 (29) of the MDR, putting into service is defined as the stage at which a medical device has been made available to the end-user for the first time on the EU market. This definition is important in the case

of in-house production since in article 5 (4) of the MDR, devices that are manufactured and used within a health institution are considered as having been put into service [1].

Article 5 (5) of the MDR establishes that the requirements for medical devices set out by the MDR do not apply to devices that are manufactured and used within health institutions in the EU, except for article 5 (5) and annex I of the MDR. Thus, the requirements for CMDs in general do not apply to CMDs manufactured within a health institution. However, the requirements established in article 5 (5) and annex I of the MDR are, nonetheless, similar to those stipulated in the MDR for "regular" CMDs, such as GSPR, QM, risk management, or clinical evaluation. The requirements discussed in section 3.1 of this thesis thus remain highly relevant for devices that are manufactured and used within health institutions, as discussed below.

Focusing on devices that are manufactured and used within health institutions, a common understanding of the term "health institution" is necessary. In particular, "health institution" is defined as any organization that has primarily the purpose of care or treatment of patients or the promotion of public health [1]. Medical devices that are produced in a non-industrial way and are used within health institutions are also referred to as in-house medical devices [75].

Article 5 (5) of the MDR requires health institutions to fulfill the following conditions and requirements to manufacture medical devices and put them into service [1]:

- The manufacturer must provide the following as established in annex I of the MDR:
    - A risk management system according to section 3.1.4 of this thesis;
    - GSPR according to section 3.1.6 of this thesis;
    - PMS and vigilance according to section 3.1.9 of this thesis;
    - Labeling and IFU according to sections 3.1.10 and 3.1.11 of this thesis;
    - Clinical evaluation (is stated in article 5 (3) as an additional requirement to annex I) according to section 3.1.8 of this thesis;
- The manufactured medical device cannot be transferred to another institution;
- The manufacturing process and the usage of the medical device are performed according to a quality management system, as described in section 3.1.3 of this thesis;
- The health institution must justify that there is no similar product on the market that meets the specific needs of patients and provides this information upon request to the BASG;
- The health institution must make a public statement with the following content:

    - The name and address of the health institution;
    - Information needed for the identification of the device;
    - A declaration, that the GSPR has been met, and if not, an adequate justification;
- The health institution provides detailed documentation to the BASG with the following content:
    - Details on the manufacturing facility;
    - Description of the manufacturing process;
    - Details on design and performance data of the manufactured medical device;
    - Specification of the intended use of the medical device;
- The health institution must take all the measures necessary to ensure that the medical device is manufactured according to the document described in the previous item;
- Finally, the health institution must review the gained experience from clinical use and take all necessary corrective actions accordingly.

As an Austrian health institution, it is, furthermore, important to consider the MPG 2021 in this regard [2]. In §9 of the MPG, it is indicated that the Austrian Federal Ministry of Social Affairs, Health, Care, and Consumer Protection can designate medical devices which may not be manufactured within a health institution. §9 MPG also allows the same ministry to provide additional requirements regarding the design, the manufacturing process, its documentation, and the QMS [2]. However, the Austrian Ministry has not specified any additional requirements yet.

In conclusion, Austrian health institutions that want to manufacture and use a CMD within their institution must fulfill the requirements listed in article 5 (5) of the MDR and consider § 9 of the MPG. Furthermore, the manufactured medical device must target patients on a non-industrial scale [75]. The manufactured device must additionally meet the patient's requirements in a way that no other medical device on the market can.

3.3. Experimental Basis – 3D Printing a Custom-Made Implant within the University Hospital Vienna

In sections 3.1 and 3.2 of this thesis, the theoretical and regulatory part of manufacturing CMDs in a health institution has been discussed. However, for a better insight into manufacturing CMDs within a health institution, a practical example is of great significance. This practical example should serve as an experimental basis and should give a better understanding of the legal

framework, regulatory requirements, and the procedure of AM of CMDs at the University Hospital Vienna (AKH). In the scope of this diploma thesis, a custom-made implant is designed and manufactured as a practical example using an additive manufacturing (AM) method. In the following sections, the procedure of additive manufacturing of a custom-made metallic implant will be discussed. Furthermore, the documentation according to the MDR for CMDs within a health institution will be elaborated. Since the focus of this thesis is on the regulatory requirements and the manufacturing process of CMDs according to the relevant standards and regulations, the following sections solely focus on the most relevant aspects of the generally broad process and methods of AM of metallic implants and the material used.

3.3.1 Introduction to Additive Manufacturing of Metallic Implants

AM, also known as 3D printing, is a series of manufacturing technologies in which a solid 3D object is formed by selective layer-by-layer apposition of a specific material according to a virtual model [4, 76]. The organization American Society for Testing and Materials (ASTM) defines AM as the following: "a process of joining materials to make objects from 3D model data, usually layer upon layer" [p. 2, 77]. In contrast to subtractive manufacturing processes, where a block of material is used and unwanted parts are removed until the desired part is left, AM starts with nothing and prints a new layer on top of the previous layer until the desired part is built [78]. Thus, this technique is cost favorable, fast, has less material wastage, and has the freedom to print complex parts [79].

There are different AM technologies which are categorized into seven groups according to the ASTM. These groups are material extrusion, direct energy deposition, binder jetting, sheet lamination, vat photopolymerization, material jetting, and powder bed fusion [6]. However, not every technology is suitable for printing metallic components for biomedical applications [6, 80]. A suitable technology, which is also used in the context of this thesis to manufacture metallic custom-made implants, is powder bed fusion. This technology includes selective laser melting.

3.3.1.1. Selective Laser Melting (SLM)

In SLM technology, metallic powder and a high-intensity laser beam are used to selectively melt and fuse the powder and create a component. As with any other AM technology, a 3D computer-aided design (CAD) is created in the first step [80]. This CAD data is converted into an STL (Standard Triangulated Language) file [6]. This data includes the actual component and some

structures, also called “Support Structures”. These support structures are in between the base plate and the component and allow easy removal of the component from the base plate of the printer after the component is printed [80]. In case of metal SLM, the support structures facilitate the removal of the introduced melt energy from the liquid metal pool.

Prior to printing, the STL file is transferred to the printer, where the fabrication of the component starts. In this regard, a thin layer of powder is spread over the base plate by the loader. As dictated by the CAD data, the laser beam melts the powder on the base plate selectively [80]. According to the layer thickness, the platform is then lowered. In the next step, the next layer of powder is spread over the previous layer. Then, the laser starts to fuse the powder again. This process repeats itself until the entire component is fabricated [80, 81]. Now, the finished component with the base plate can be taken out and separated [80].

For this complex procedure, hundreds of parameters must be correctly optimized since their influence has a huge impact on component quality [6, 81]. Some of the most influential and researched parameters for SLM printers are laser power, laser scan speed, hatch distance, hatch style, layer thickness, powder particle size, and the mechanical properties of the powder [6, 80]. These parameters are optimized by machine manufacturers to produce a dense material, minimize defects, reduce surface roughness, and increase the build rate [82]. Parameters related to the mechanical properties of the used powder have also a crucial role in the quality of the printed component. These parameters are melting point, density, latent heat of fusion, thermal conductivity, heat capacity, and melting enthalpy [80].

A powder material, which has high strength, good corrosion resistance, and is biocompatible, is titanium. One of the most used titanium alloys, which is also used in the aerospace industry [23], and is called a “workhorse alloy” is Ti-6Al-4V [83]. This titanium alloy consists of 6% aluminum and 4% vanadium [6] and is used for traumatology implants since it has high yield strength and fast osseointegration [81]. However, it must be highlighted that Ti-6Al-4V is not considered to be safe for long-term use, since the release of aluminum and vanadium ions can cause neurological disorders [84].

In the context of this thesis, the SLM printer SLM 125 from SLM Solutions Group AG (Germany, Lübeck) is used [85]. Furthermore, the titanium alloy Ti-6AL-4V ELI (Grade 23) from SLM Solutions Group AG, with a building envelope of 125x125x125 mm, is used [86]. In the datasheet

of the titanium alloy powder, the mechanical properties, such as tensile strength and elastic modulus, are indicated [86]. Further information regarding the SLM 125 machine and the used titanium alloy powder can be taken from the IFU of the device and the material data sheet of the powder [85, 86].

3.3.1.2. Additive Manufacturing in Healthcare Applications

Over the past 15 years, AM has become an important application in the field of healthcare [4]. AM is used in a wide range of applications such as restorative dentistry, orthodontics, neurosurgery, oncology, oral and maxillofacial surgery, and orthopedic surgery [87]. More and more researchers and surgeons use AM to manufacture complex custom-made orthopedics and maxillofacial implants [88]. In this regard, AM is used for bone and dental reconstruction or stabilization, which has shown an improvement in mobility and quality of life [4]. This technology allows the designing and manufacturing of implants which have customized sizes, shapes, and mechanical properties for a specific patient [88].

The MDR defines an "implantable device" as any device (including an absorbable device) which is intended to be totally introduced into the human body by clinical intervention. This also includes devices that are partially introduced into the human body and remain there for at least thirty days [1]. The chemical properties of implants must be in such a way that it does not affect the infiltration and nutrition transport and they must avoid immunological response and corrosion. Furthermore, the mechanical properties of implants must be adjusted so that it ensures no movement or fracture of the implant [84]. With the help of AM, these implants can accurately be adjusted to the clinical need of the patient [87].

3.3.1.3. Process of Additive Manufacturing for Biomedical Implants

The process chain of additively manufactured implants typically starts with taking the 3D imaging data of the patient with computer tomography (CT) scanning [6, 89]. In a CT scan, an X-ray beam is used to capture detailed information on the density of the bone, spine, and other inner parts of the body at different levels. For detailed information regarding the soft tissue of the body, magnet resonance imaging (MRI) with high magnetic fields and radio frequency pulses, can be used to capture structures such as joints or the brain. To manufacture a patient-specific orthopedic implant by AM, CT and MRI, therefore, play a significant role in the process chain of implant design [89]. These image slices are usually stored in Digital Imaging and Communications in Medicine

(DICOM) format, according to the international standard ISO 12052 for medical images and associated information [90].

In the next step, a software is used to create a 3D virtual model of the images captured from CT and/or MRI. Such a software is Mimics (Materialise, Lueven, Belgium), which is also used in the course of this thesis. To create the 3D virtual model, the anatomical part, which is necessary for the implant, is segmented from the surrounding tissues [89, 90]. Segmentation in Mimics is done by the following steps: adjusting the image orientation, data preparation, and filtering, specifying the threshold, region growth, and 3D model reconstruction. The constructed Computer-Aided Design (CAD) 3D model is exported to 3-Matic software to design the implant [90]. In this step, a reasonable and patient-specific implant can be designed that depends on the anatomical part and structure of the patient [89]. For step-by-step instructions and the designing of the implant, documents such as the release notes from Materialise [91], or the paper from Feng, et al. [92], offer further guidance.

The CAD implant is then converted to an STL file. Considering the parameters of the SLM 125 machine, which is given by the manufacturer, the design implant can be printed [82]. After the implant is printed and removed from the base plate, the residual powders which have not been melted must be cleaned [78].

In order to improve the surface topology, the biological performance, and the mechanical properties of the printed implant, post-processing steps are required. The post-processing steps considered for this thesis include hot isostatic pressing, sandblasting, and sterilization, which will be further discussed in section 3.3.5 of this thesis. In the last step, the printed and post-processed implant must be investigated to characterize the surface morphology, microstructure, and fracture surface of the printed implant [93]. This step is discussed in section 3.3.6 of this thesis.

Figure 3 shows the procedure of industrial additive manufacturing a titanium implant. In this figure, the procedure is presented as a cycle, starting at the clinical assessment step, which takes place between the hospital/research center and the industry [6]. The aim of this diploma thesis is, however, to establish the possibility to manufacture CMDs at the health institution, without the participation of the industry.

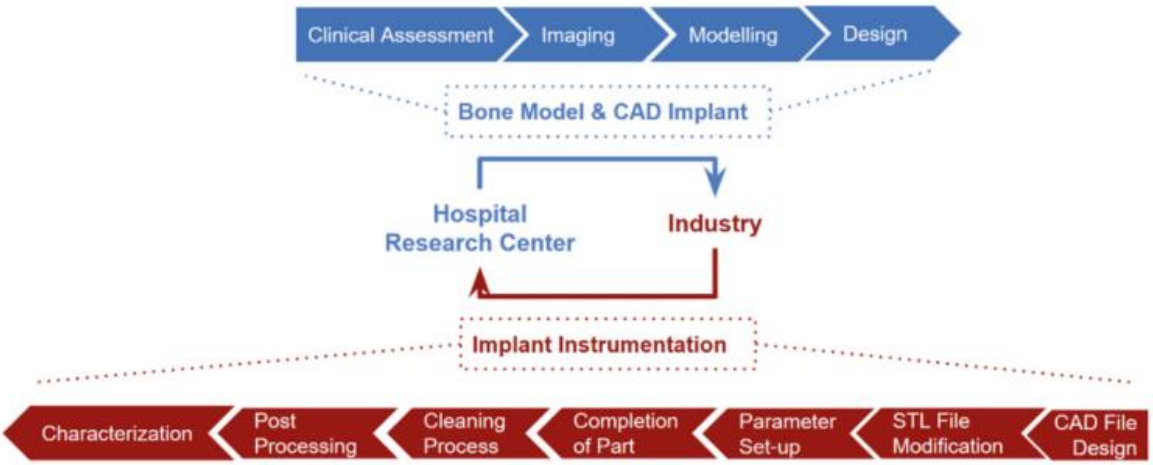

Figure 3: Manufacturing procedure between hospital and industry for an additively manufactured implant [6].

To demonstrate the safety, efficacy, and compliance with regulatory requirements of implants made according to the procedure in figure 3, standards can be used. As discussed in section 2.5 of this thesis, there are two organizations (ASTM and ISO) that utilize the expertise of AM practitioners worldwide to develop standards needed for AM [28]. These relevant standards for additively manufactured Ti-6AL-4V ELI (Grade 23) implants using an SLM printer are discussed in section 4.2 of this thesis.

In the next section, the example of use that is used in this thesis as a practical example in order to explain the process of manufacturing a 3D-printed CMD in the Vienna University Hospital (AKH) and the related regulatory requirements are discussed.

3.3.2 Introduction to the Example of Use

In this section, the example of use that is chosen to explain the procedure of additive manufacturing of a CMD within a health institution is discussed. In this regard, a CMD is printed with the SLM 125 printer which is located at the CMPBME at the Medical University of Vienna. The material used for printing these CMDs is the Ti-6AL-4V ELI (Grade 23) powder, as mentioned in the previous section. The printed CMD is a subperiosteal implant, also referred to as CMSI, which will be explained in the following.

To understand the printed CMD, the anatomical structure of the upper fixed bone of the jaw, which is also called the maxilla, is briefly explained. A maxilla consists of two bones (maxilla proper and premaxilla) which, during fetal development, fuse together at the incisive suture. These two maxillae form the upper jaw, the middle face, and the hard palate. The shape of the maxilla is

pyramidal and hollowed and it carries the upper row of teeth and transfers the masticatory pressure to the cranium with a frontal and a zygomatic arch abutment [94, 95]. The periodontium attaches the teeth to the maxilla and gives an elastic support that withstands functional forces. The periodontium consists of the cementum, alveolar bone (both hard connective tissue), periodontal ligament, and gingiva (both soft connective tissues) [96]. Figure 4 shows the cross-section view of a tooth [97]. In this figure, the attachment of the cementum to the alveolar bone can be seen.

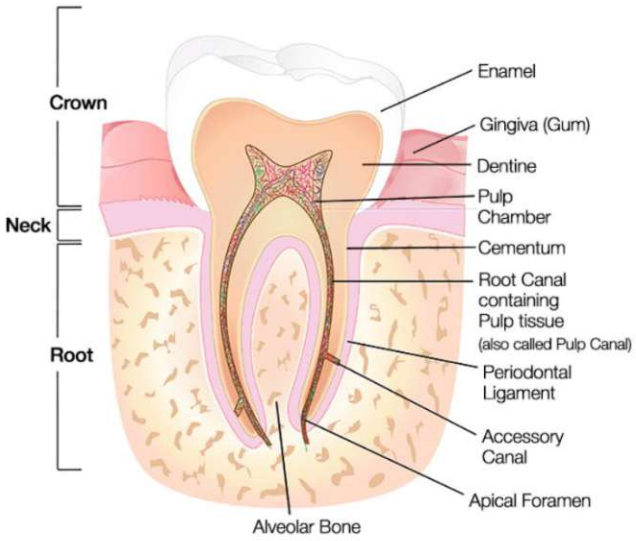

Figure 4: Anatomical structure of a tooth [97].

Due to diseases (dental caries, periodontal diseases, or cancer), however, the teeth can be loosened and eventually lead to an edentulism condition, in which the natural teeth fall out of the maxilla [98]. After the loss of the natural teeth, no further force is applied to the alveolar bone. In this condition, the alveolar bone starts to degrade [96]. A possible rehabilitation solution for this condition is an endosseous (endosteal) dental implant [99]. Endosteal implants are inserted into the alveolar bone. Therefore, a reasonable amount of bone in quantity and quality is required. For patients with severe bone atrophy, several techniques for bone regeneration such as bone grafting, guided bone regeneration, alveolar ridges split, distraction osteogenesis, and maxillary sinus augmentation exist [99]. A known and excellent rescue option for edentulism is a custom-made subperiosteal implant (CMSI) that is also designed and manufactured in this thesis [100]. This dental implant is placed between the residual alveolar bone and the periodontal ligament, and usually has transmucosal elements which are extended into the oral cavity and connect the implant to the prosthesis [99]. Figure 5 shows an example of an additively manufactured custom-made subperiosteal implant as a 3D reconstruction [101]. The size and shape of a custom-made

subperiosteal implant depends on the patient condition and can be adapted accordingly (note the definition for CMD in section 2.3 of this thesis).

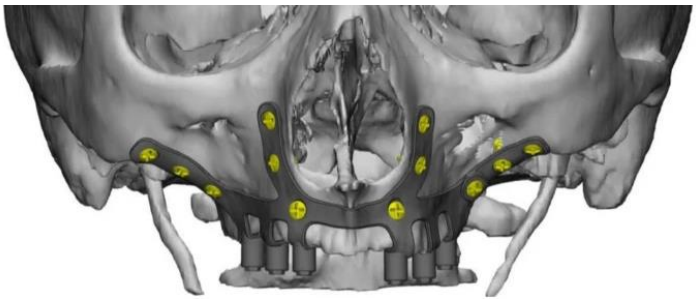

Figure 5: An example of a Custom-Made Subperiosteal Implant [101].

These subperiosteal implants also contain mini-screws that secure the implant to the bone. In this regard, two different types of screws exist. The so-called self-trapped screws (STS) need a prior preparation of a hole with drills whose diameter corresponds to that of the screw core. The other type of screws for fixing the implant on the bone are drill-free screws (DFS) [102, 103]. The DFS has a tapered core with threads that allow the screw to be self-drilling and self-tapping. Figure 6 shows these two different types of screws [102].

Figure 6: An example of the self-trapped screw (left) and a drill-free screw (right), each 2 mm in diameter and 6 mm in length [102].

According to the papers from N.M. Hiriyanna, et al., and B. Sancar, et al., there is no difference regarding the failures or fragment stability between STS and DFS [102, 103]. These screws are not designed and manufactured for this thesis, since they can be bought commercially.

In the context of this diploma thesis, a custom-made subperiosteal titanium (Ti-6AL-4V ELI - Grade 23) implant is printed with the SLM 125 printer at the CMPBE to depict the process of AM considering the available resources at this center, the MDR, and relevant standards. For the customization of the subperiosteal implant, CT scan data from an anonymized patient, which has already been segmented with Materialise, was used[1]. Since in this diploma thesis, the consideration

[1] This model was also used in the diploma thesis from Daniel Alexander Aigner, "Design and Optimization of a Patient-Specific Additively Manufactured Subperiosteal Ceramic Implant " [103].

will only be on the maxilla of the patient, the remaining part of the head is removed with 3-Matic (Materialise) to save data processing and material for the printing of the model. The maxilla, for which the subperiosteal implant will be designed, is shown in figure 7.

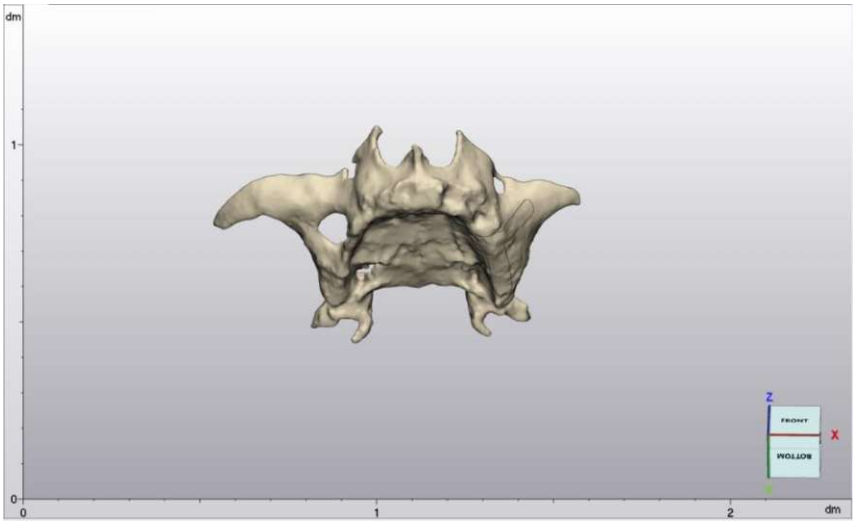

Figure 7: Bottom part of Maxilla of an anonymized patient [104].

This model from figure 7 is also printed for the validation of the implant. This printing is done with a Fused Deposition Modeling (FDM) printer at the CMPBME.

For this example of use, a case management file with relevant case documents is stored and access is restricted. This allows to maintain the confidentiality of the patient [105]. In the following, the procedure (design, manufacturing, post-processing, and material/product characterization) of AM of this example of use is discussed.

3.3.3 Design Procedure of the Subperiosteal Implant

The above-mentioned model (figure 7) is used to design the custom-made subperiosteal implant (CMSI). The procedure of designing a custom-made implant is challenging and relevant design rules and standards are considered in this thesis [106, 107]. Such design rules are, *inter alia*, part orientation, wall thickness, and size between features or holes and channels [107]. These rules are listed in the doctoral thesis of Daniel Thomas [107] which is also referred to in the ISO/ASTM 52911-1:2020 standard [108]. This standard specifies design recommendations for Laser Powder Bed Fusion of Metals (LPBF/M). Another standard in relation to the design for AM is the ISO/ASTM 52910:2022, which gives general recommendations for using AM in product design [109]. The above-mention work from Daniel Thomas and the standards were analyzed for the designing of the CMSI.

Furthermore, the design must consider the anatomical, biological, functional, and aesthetic requirements [110]. For these requirements, no standard is available yet from the ASTM F42 committee. However, several papers such as the work from S. Barone et al. [110] and A. Surovas et al. [111] state the main points for designing a dental implant for AM. In the following, the above-mentioned aspects regarding the design of additively manufactured (LPBF/M) dental implants are discussed and an interesting design control procedure from R.J. Morrison [7] is shown.

Before starting to design an implant, it is important to get familiar with relevant standards in this field. The ISO/ASTM 52910:2022 provides requirements, guidelines, and recommendations for the designing of parts to be manufactured by AM processes in general [109]. It starts with giving an overview of design opportunities and limitations and continues with product considerations such as design effectiveness, product consolidation, assembly features, multi-part mechanism, geometrical considerations, and material property considerations. Furthermore, the standard discusses the possible environmental (e.g., biological exposure) of the manufactured product, to consider the exposure effect already in the design process [109]. Additionally, sustainability and business considerations are discussed in the standard. At the end of the ISO/ASTM 52910:2022, important warnings for designers are listed that need to be considered before starting with designing an implant [109].

Another relevant standard that extends the scope of ISO/ASTM 52910:2022 is ISO/ASTM 52911-1:2020. This standard gives design recommendations for metallic products, such as custom-made subperiosteal titanium implants, which are manufactured through the LPBF technology. This standard discusses the build orientation, positioning, and arrangement of the product and explains the design rules [108]. In this regard, ISO/ASTM 52911-1:2020 also refers to the work of Daniel Thomas [107]. These design rules are part orientation, geometric compensation, surfaces in every direction, size and thickness, chamfers and radius, geometric structure, supporting, pilot drilling, and reaming accurate holes and threads [107, 108]. Numerous experiments were done in this regard to provide a production appropriate range of geometric design features [112]. J.W. Booth et al. [113] present a worksheet called Design for Additive Manufacturing (DfAM) which can be used as a checklist to validate the design and to check whether it is manufacturable or not [112]. All the relevant requirements from these standards are analyzed and considered for the designing of CMSI in the course of this thesis. Thus, every step from the standards is studied and important design recommendations for the CMSI are implemented in this thesis.

An important consideration during the designing of implants are the anatomical, functional, and aesthetical requirements. In this regard, the implant position, bone density (for screw positioning), and teeth distance must be analyzed to design an implant that fits the anatomical structure of the patient [110]. Furthermore, the number of abutments for support and fixation of dental restoration is also important [106]. Since the perforation in the mouth, and thus the implant-epithelial junction, can lead to bacterial invasion and loosening of the implant, the number of abutments must be as low as possible to keep the perforations low in the mouth. Furthermore, narrow spaces, crevices, and concavities must be avoided to hinder contamination and allow regenerative processes [111]. To design a safe and functional implant with the appropriate quality, the engineer and the surgeon must work together [114]. For these considerations, no standard is available yet. Therefore, collaboration with the responsible physician or surgeon is necessary to avoid complications. For the CMSI designed and printed in the course of this thesis, the important points regarding the anatomical, functional, and aesthetical requirements as established in the literature are considered.

Since avoiding design errors in the early phases of manufacturing would save time and money, a process for the design procedure is developed. A systematic design development that helps to identify design flaws and the verification and validation of design efficiency is the design control model. This model consists of the user needs, design input, design process, design output, and design verification and validation as shown in figure 8 [7].

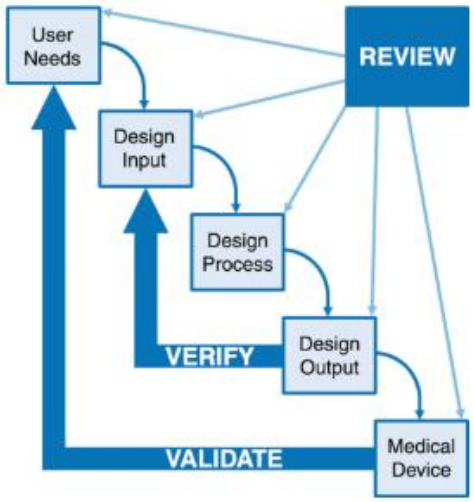

Figure 8: Design control model [7].

This documented manufacturing process, which covers the steps from imaging to the STL file, is crucial and must be reviewed by the surgeon or a peer, as shown in figure 8. Furthermore, the classification, the risk assessment, and the GSPR checklist with the requirements for the medical device must be created at the start of the project [105]. For the CMSI designed and printed in the course of this thesis, the procedure from figure 8 is used to verify and validate the CMSI. Furthermore, the patient's need is identified and the implant is designed. Thereafter, the design is verified by applying the designed CMSI (figure 11) to the model (figure 7) in the software Materialise. After the design is verified, the printed medical device is validated. This is done by applying the printed CMSI to the model and checking the functionality, aesthetics, and anatomical position. Furthermore, software-based mechanical testing can be performed to test the mechanical properties of the CMSI.

In this thesis, the design is performed considering the above-mentioned standards and recommendations from academia. Accordingly, the maxilla model from the previous section (figure 7) is opened with 3-Matic and the implant is designed. In this regard, the reference guide for 3-Matic from Materialise is used [115]. Furthermore, the design is verified to identify flaws and to correct them already in 3-Matic. The results of the design of the created implant are shown in section 4.3.1.

3.3.4 Additive Manufacturing of the Subperiosteal Implant

This section elaborates on the printing of the reviewed and verified design, as discussed in section 3.3.3, with the SLM 125 printer at the CMPBME. In this regard, communication with the operator, who is allowed and trained to use the SLM 125 printer, is important. For the manufacturing of the implant, the instruction for use (IFU) of the SLM 125 printer is observed and the validation is done according to figure 8 [116].

According to the IFU of the printer used, only a person who has received a briefing from an SLM employee is allowed to use the SLM printer. Additionally, a person can be trained to assess hazards related to the SLM printer [116]. At the CMPBME, the operator is trained according to the DVS® 3602, is a specialist in metallic additive manufacturing processes, and is additionally briefed by an SLM employee. Thus, this person is familiar with the procedure of the printer and shall document the status of the printer, take care of the printer, and document the traceability of the machine. In

this regard, the maintenance and calibration process of the SLM 125 must be documented and traceable [105].

As discussed in section 3.3.1.1 the parameters of the SLM 125 printer must be tuned according to the application to ensure the quality of the implant. The parameters of the SLM 125 printer at the CMPBME are tuned by the manufacturer of the printer to ensure the quality of the implants. However, for future projects, these parameters must be adjusted according to the application or product [114].

The procedure of printing is performed with the presence of a specialist (an employee of the Medical University of Vienna) in accordance with the IFU of the SLM 125 printer. The procedure of printing consists of preparation of the powder, switching on the machine, preparing the build process, executing the build process, and following up the construction process, as described in the IFU of the printer [116]. For the printing of the CMSI, the SLM specialist prepared the previously created design on the SLM printer and printed the sample. Furthermore, with the presence of the SLM specialist, the printed CMSI is removed with the plate from the SLM printer. During this procedure, printer safety and personal protective instructions are considered according to the IFU of the printer [116]. To ensure the quality of the printed implant, a work instruction for manufacturing with regard to safety aspects and the IFU of the printer must be developed by the specialist and the quality manager of the CMPBME [105, 114].

Another important quality aspect during manufacturing with the SLM 125 printer is real-time process monitoring [112]. This monitoring system allows a high degree of process documentation and verification and consists of Melt Pool Monitoring (MPM), Laser Power Monitoring (LPM), and Layer Control System (LCS). The latter is a testing and documenting system that inspects the performance of each layer by detecting coating irregularities [117]. Thus, printing failures such as porosity, residual stresses, cracking and delamination, balling, geometric defects, and dimensional inaccuracy can be observed [112]. The LCS is available for the SLM 125 at the CMPBME and is used according to the IFU of this software [118].

After the implant is successfully printed, post-building activities, such as removing the base plate, cleaning off the loose powders, or separating the implant from support structures, according to section 6.2 of ISO/ASTM 52908:2022 is performed [119]. Furthermore, the implant is validated according to figure 8 to ensure that the patient's requirements are met. This is done by testing the

printed implant on the available maxilla model. For validation, the presence of the designer and surgeon is important. When improvements are required, the process starts from the beginning (user needs) of figure 8 [7]. Otherwise, the post-processing can be started.

3.3.5 Post-Processing Steps of Subperiosteal Implant

In this section, the post-processing activities for the additively manufactured (LPBF/M) subperiosteal titanium implant are discussed. These activities are done before the final inspection and characterization [119]. The as-built printed implant from the SLM 125 printer must go through post-processing applications to get higher cellular activities and reach closer bone mechanical properties [6]. In this regard, the standards ISO/ASTM 52908:2022, ISO 10993-2018, ISO 20160:2006, and state-of-the-art papers such as the paper from F.N Depboylu et al. (2022) [6], A.N. Aufa et al. (2022) [81], and the book section from S. Bagherifard and M. Guagliano (2021) [120], are considered to choose relevant post-processing steps for the example of use from this paper. It is worth mentioning that at the time of writing of this thesis, no standard from the F42 committee regarding the post-processing of implants manufactured with the SLM printer (with Ti-6AL-4V ELI (Grade 23)) is available.

Even though AM is a convenient manufacturing method to print complex and customized implants, challenging post-processing steps are required to improve the surface topology, biological performance, and mechanical properties in their applications [93]. Post-processing includes heat treatment, surface treatment, and sterilization which will be explained in the following [121].

3.3.5.1 Heat Treatment:

During the manufacturing of the implant, a high temperature gradient is applied in the SLM 125 printer, which leads to microstructural features and grain size irregularity [120]. This rapid heating and cooling also lead to undesirable residual stress [78]. Furthermore, residual pores are formed during manufacturing due to entrapped gasses, lack of fusion, or pores caused by the movement of the laser source, which leads to a bad fatigue performance [93, 120].

A method that is used to improve the material properties of the as-built implant is heat treatment. Heat treatment can homogenize the microstructure of the implant and increases the isotropy. Furthermore, appropriate heat treatment relieves the residual stress in the as-built implant [120]. In the case of titanium, heat treatment is usually performed in a vacuum furnace and the temperature is at 800°C for 2h [122]. The normal heat treatment, however, cannot eliminate the porosity of the

manufactured implant. A heat treatment method, which also induces pore closure in the implant, is hot isostatic pressure (HIP) treatment. In HIP treatment, the implant is exposed to high temperature and at the same time the gas pressure is held isostatically [120]. HIP is usually performed at 930°C with a gas pressure of 100 MPa for 4 hours [93]. The customer information document from SLM Solutions Group AG recommends a HIP at 940°C for 4 h in argon for Ti6Al4V ELI (Grade 23) [86]. According to ISO 52908:2022, the following points should be considered during the heat treatment: reducing residual stresses, reducing anisotropy, densification, and preparation of the material for mechanical post-processing [119].

At the CMPBME the HIP procedure cannot be performed since the equipment is not available. However, the CMPBME has a laboratory furnace chamber from the company Linn High Therm which reaches a temperature of 1340°C. Since this chamber is currently being installed and cannot be yet used at the CMPBME, this process is only discussed in theory and could not be tested in practice as part of this thesis.

3.3.5.2 Surface Treatment:

Depending on the application of the manufactured product, suitable surface treatments must be chosen [119]. In the field of dental implant application, the bounding between the bone and the implant is affected by the material used and the surface of the manufactured implant. Therefore, surface treatment is done to improve the biological performance and the interaction between the implant and the surrounding bone. Furthermore, surface treatments are essential to get an implant with high structural integrity [93]. To remove the residual particle powder which is only partially melted on the surface and to reduce the surface roughness of the implant, sandblasting (SB) is used [93, 120]. Depending on the size of the printed implant and the blasting gun, SB is usually done for 30 min and at a speed of 100 m/s.

Another possible surface treatment, which is done after HIP, is chemical etching (CE) [93]. CE is done usually with nitric acid and hydrogen fluoride solutions and can also remove loose powders from interconnected lattice-like structures [6]. According to P. Jamshidi et al. [93], applying HIP followed by CE is the best method to improve fatigue performance and enhance cellular affinity when tissue integration is needed [6, 93]. Furthermore, surfaces that come in contact with soft tissues are usually preferred to be polished.

Another surface treatment, which is still in development, is organic and non-organic coating [122]. According to E. Chudinova et al. [123], a coating that is widely used and makes the implant more biocompatible and accelerates the recovery process is hydroxyapatite and calcium phosphate [122]. Also, in this case at the CMPBME, an SB machine is being installed but is not operative yet. Therefore, it cannot be used for the printed implant in this diploma thesis.

3.3.5.3 Sterilization

To minimize the risk of infection, the implant needs to be sterilized before the surgery. Depending on the material used, an appropriate sterilization method is used [7]. In D. F. Angelo et al. [100], for instance, the Ti6Al4V printed subperiosteal implant is sterilized with ethylene oxide before the surgery. Since the sterilization unit of the AKH is certified according to ISO 13485, the sterilization and verification of the printed implant can be done by this unit. The sterilization method depends on the material and is set by the sterilization unit [105].

The above-mentioned post-processing treatments need to be validated by establishing objective evidence that the final printed implant meets user needs, the intended use, and is safe for the patient. In this regard, several characterization methods and testing must be performed [7].

3.3.6 Material Characterization and Testing of the Subperiosteal Implant

The titanium alloy used for the CMSI printed in the course of this thesis usually has a high corrosion resistance, is biocompatible, and has a low elasticity compared to co-based alloys or stainless steel. The surface properties of the printed implant affect the corrosion properties, cell adhesion, protein adhesion, proliferation, and lifetime of the implant in vivo [124]. Therefore, in this section, the printed Ti6Al4V ELI implant is analyzed to determine its characteristics.

First, relevant standards (e.g.: ISO/ASTM 52907:2020 [125]) are considered to analyze technical specifications for the used metallic powder. After the manufacturing of the implant with the SLM printer, the surface characteristics must be analyzed. For this purpose, Scanning Electron Microscopy (SEM) can be used [93]. Furthermore, mechanical validation should be considered. Depending on the application, the implant can go through mechanical testing such as compression, three-point bending, and open-angle displacements to meet the user's criteria [7]. In this regard, the Finite Element Method (FEM) can be used as an alternative method to perform software-based mechanical testing [7, 126]. At the end of this section, the biological evaluation of the printed

implant is discussed using the harmonized standard ISO 10993-1:2020 and the non-harmonized standard ISO 7405:2019 which is for medical devices used in dentistry [127, 128].

The used Ti6Al4V titanium alloy is the most used alloy in automotive and aerospace and due to its biocompatibility, it is also used in the biomedical industry [86]. During the SLM manufacturing process, the Ti6Al4V powder is melted and solidified into an implant. Thus, the quality of the powder has an important effect on the surface quality, geometry, dimensional accuracy, and mechanical properties of the implant. While the unused powder yields the best results regarding these parameters, the already-used powder shows alteration in its properties [114]. It is shown that after 15 repetitions of 3D printing with the same powder, a significant change can be seen. Figure 9 shows an SEM image of an unused powder versus powder that has been used 15 times.

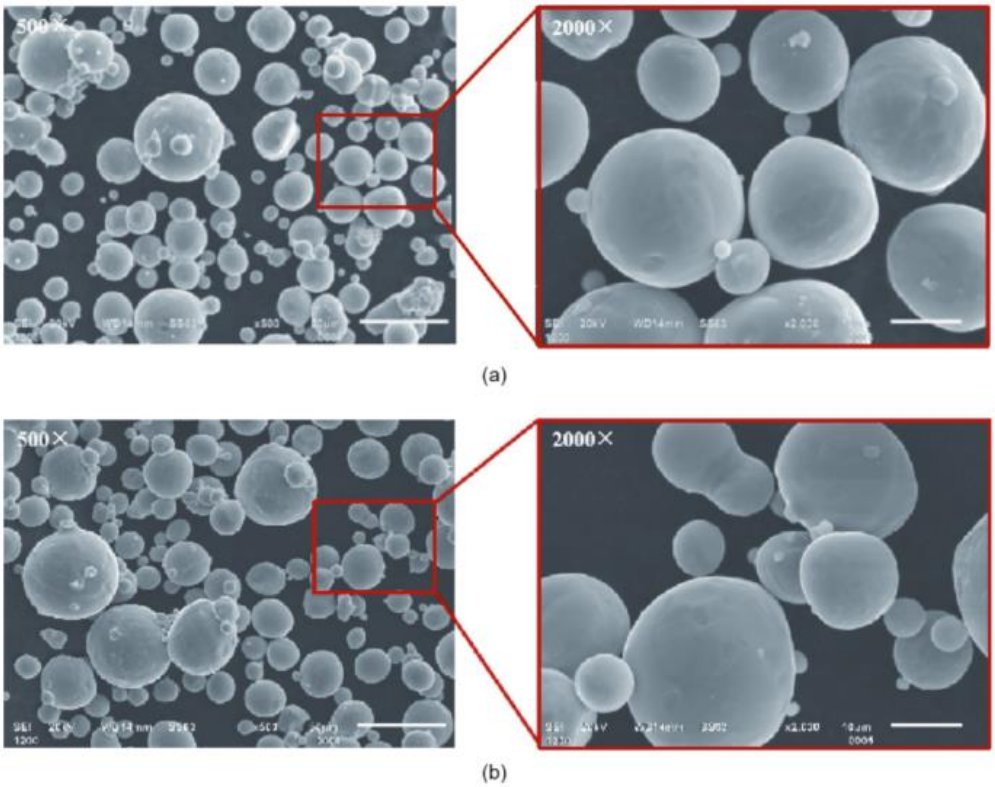

Figure 9: SEM image of a) unused powder versus b) a used powder [114].

Figure 9 shows that the shape of the powder changes after 15 recycles [114]. Thus, the powder quality, including particle size, particle distribution, chemical composition, characteristic densities, morphology, flowability, and contaminants, must be checked according to the standard ISO 52907:2020 [114, 125]. Additionally, the SLM 125 printer at the CMPBME contains a Manual Powder Sieve, which sieves and separates metal powder [129].

In addition, SEM can be used to analyze the surface of the printed implant. An example of a printed Ti6Al4V sample can be seen in figure 10. In figure 10a, the as-built sample can be seen. On the sample in figure 10d HIP, SB, and polishing are performed [93]. Furthermore, a surface profilometer or an Atomic Force Microscopy (AFM) can be used to investigate surface roughness, since surface roughness is important for cell activity [124]. A standard that can be used to classify the microstructure of titanium alloys, is ISO 20160:2006. This standard provides a catalog of metallographic photomicrographs which serve as an aid in the communication on types of microstructures of titanium implants [130]. For the surface analysis of the as-built CMSI designed and printed in the course of this thesis, a 3D measurement system head (VR-5200) from the company Keyence is used. The results are shown in section 4.3.2 of this thesis.

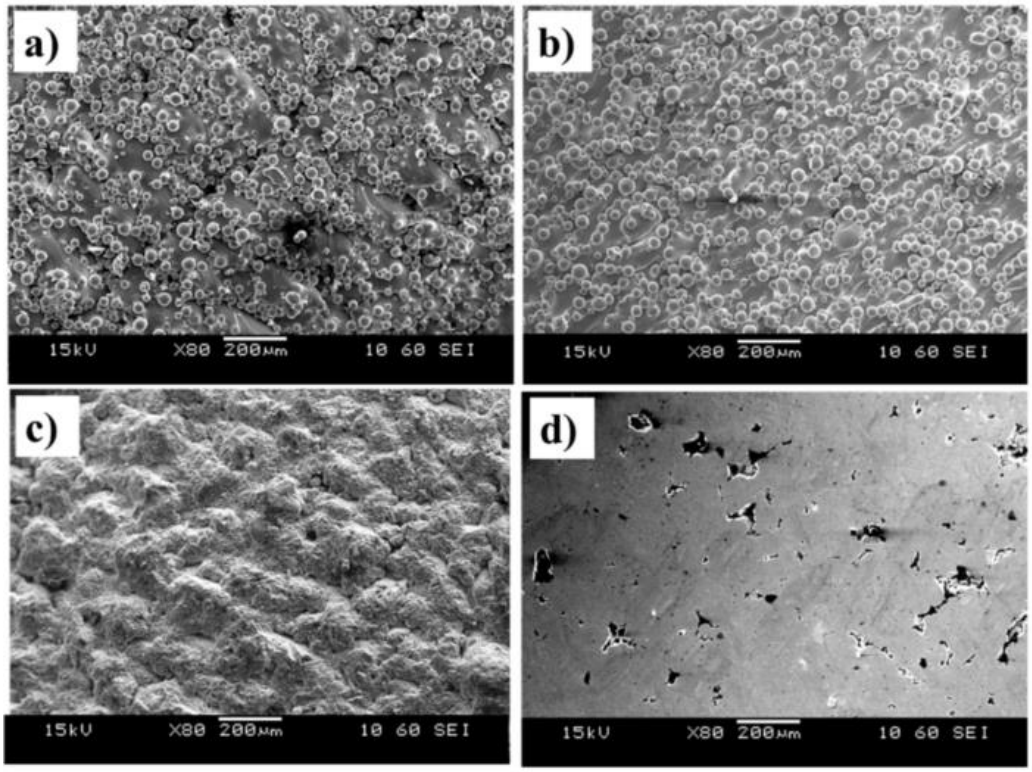

Figure 10: a) as-built sample, b) HIP performed, c) HIP + SB is performed, d) HIP + SB + polishing [93].

Besides surface and powder characterization, defectoscopy can be used to detect air bubbles or foreign materials in the implant. This is done by using industrial CT, where pores in size of 0.3 mm can be detected [131].

Depending on the application of the implant, different mechanical properties of the printed implant can be determined using different testing methods such as the three-point bending test, the compression test, or the tensile test [7]. These tests can be performed on the printed implant.

However, since the printed implant might have a complex structure, the clamping of the implant on the grips of the testing machine and the boundary condition of the implant are difficult to fulfill. Therefore, a sample (also known as dog-bone) for mechanical testing only can be printed with the SLM 125 printer at the CMPBME [132]. The ASTM E8/E8M – 15a standard can be considered for the size of the sample and the tensile testing. The tensile test according to this standard will prove the yield strength, yield point elongation, and tensile strength [133].

In the case of the SLM 125 printer at the CMPBME, a datasheet for the Ti6Al4V ELI (Grade 23) powder is provided by the SLM manufacturer which states the mechanical properties of that powder. For example, the tensile strength and the elastic modulus of the used powder are 1281 MPa and 113 GPa respectively [86]. Since the CMPBME at the Medical University of Vienna has no access to testing facilities for tensile and compression tests, these tests must be performed by external providers [105].

Alternatively, the so-called FEM can be used to determine the mechanical properties of the implant. This software-based stimulation of the implant with the simulation of external loads (according to the application) can be used to represent the stress field distribution on the implant. Knowing the tensile strength and the elastic modulus of the used material (from datasheet), the stiffness and strength can be calculated [126].

Finally, the biological effects of the manufactured implant must be evaluated to protect humans from risks arising from the implant. In this regard, the harmonized standard ISO 10993-1:2018 and the non-harmonized standard ISO 7405:2019 can be applied [127, 128]. This evaluation can be done by external providers, who are certified to perform these evaluations according to ISO 10993-1:2018.

At the CMBME, a wide-area 3D measurement system head (VR-5200) from the company Keyence is used to analyze the surface (roughness) of the printed implant. With this measurement system, shape deviations can be inspected and the as-built implant, as well as the post-processed implant, can be compared [131].

3.4 Development of Standard Operating Procedure for 3D Printed Titanium Custom-Made Implants at the Vienna General Hospital (AKH)

As discussed in section 3.1.3 of this thesis, medical devices have to be manufactured according to a relevant QMS such as the ISO 13485:2016. QMS standards such as ISO 13485:2022 require a

documented process description for the procedure of the production of medical devices. These documents must be traceable [45]. In this regard, a flowchart according to ISO 5807 for the AM process of medical devices at the CMPBME is created in the course of this thesis and presented in section 4.4 of this thesis [134]. This process is mainly related to the procedure of SLM printing with the SLM 125 at the CMPBME, the used Ti6Al4V ELI (Grade 23), and the available facilities at this center.

Since there are no official process requirements from the European Commission in this regard, relevant publications, in particular from K. Willemsen et al. [8], R.J. Morrison et al. [7], and R. Du et al. [114], are analyzed and considered to draft a Standard Operation Procedure (SOP). These three publications are of particular importance since they give a profound understanding of the procedure of AM and the relevant quality control. Another consideration in the preparation of the SOP is the document on technical considerations for AM medical devices from the U.S. Food and Drug Administration (FDA) [135]. Furthermore, relevant standards from ISO and ASTM must be considered for this process and are thus discussed in further detail in section 4.2 of the thesis.

A process consists of an input, an output, and the processing activity itself, whereby the process can be steered, as elaborated on in section 4.4. Every step of the process drafted in the course of this thesis as depicted in section 4.4 can consists of several different sub-procedures with respectively different work instructions which need to be documented. For example, the step of "printing" also consists of the procedures for powder management and the procedure for the maintenance of the SLM printer. For powder management, different work instructions, such as the exchange of the used powder or quality control of the used powder (according to standards), exist. This thesis, however, focuses on the main process of manufacturing. Thus the relevant sub-procedures and work instructions of each step are solely mentioned briefly and are not explained in further detail since this would exceed the scope of this thesis.

Concentrating on the main process of manufacturing, section 4.4 will further elaborate on the respective steps. It is, however, important to highlight beforehand that these steps must be reviewed by the surgeon and the manufacturing team, and, if necessary, improved. In this regard relevant documents such as the technical file, risk management, process description, and other requirements from the MDR, as elaborated on in sections 3.2 and 4. of this thesis, must be saved and accessible for the manufacturing team and the surgeon. It is also worth mentioning that the general hospital

of Vienna (AKH) is certified according to ISO 9001 [136]. Since the CMPBME is a part of the AKH, the processes of this center are documented and reviewed by the quality management team. Therefore, the process of AM of medical devices with the SLM printer as developed in this thesis can become a part of a quality management processes at the CMPBME.

4 Results

As discussed in the chapters "Introduction" and "Methods", the focus of this thesis lies on the regulatory requirements and the quality control of CMSIs manufactured with an SLM printer within a health institution. Therefore, all the regulatory requirements needed to manufacture a CMSI and to put it into service are explained in the chapter "Methods". Furthermore, the chapter "Methods" discusses the techniques used to print such a CMSI, considering relevant standards and quality assurance. To provide a practical example and thus a profound understanding of the central elements of the process of manufacturing a CMSI with an SLM printer at a health institution, extensive supplementary documentation on the Classification, Risk Management, and GSPR is produced and compiled in an additional work named "Selected Regulatory Requirements for a Custom-Made Subperiosteal Implant" (in the following: supplementary documentation) [54]. Based on a practical example (section 3.3), this thesis, furthermore, establishes an SOP in section 4.4, to enable a process-oriented manufacturing of 3D-printed custom-made implants. In addition, this thesis not only provides research on the relevant (harmonized) standards but also establishes a list of the relevant standards in table 3 of section 4.2, to ensure the conformity of the CMSI with the legislation and provide a practice-oriented overview of the respective legal requirements for the manufacturing a CMSI with an SLM printer at a health institution. Besides, this thesis also discusses the remaining aspects of the regulatory requirements and quality assurance of the in-house production of a CMSI in theory in sections 3.1.1 to 3.1.11, 3.3, and 3.4. In brief, figure 11 lists the steps that are performed practically in the course of this thesis (i.e., the results) in green and those, which are discussed in theory, in black.

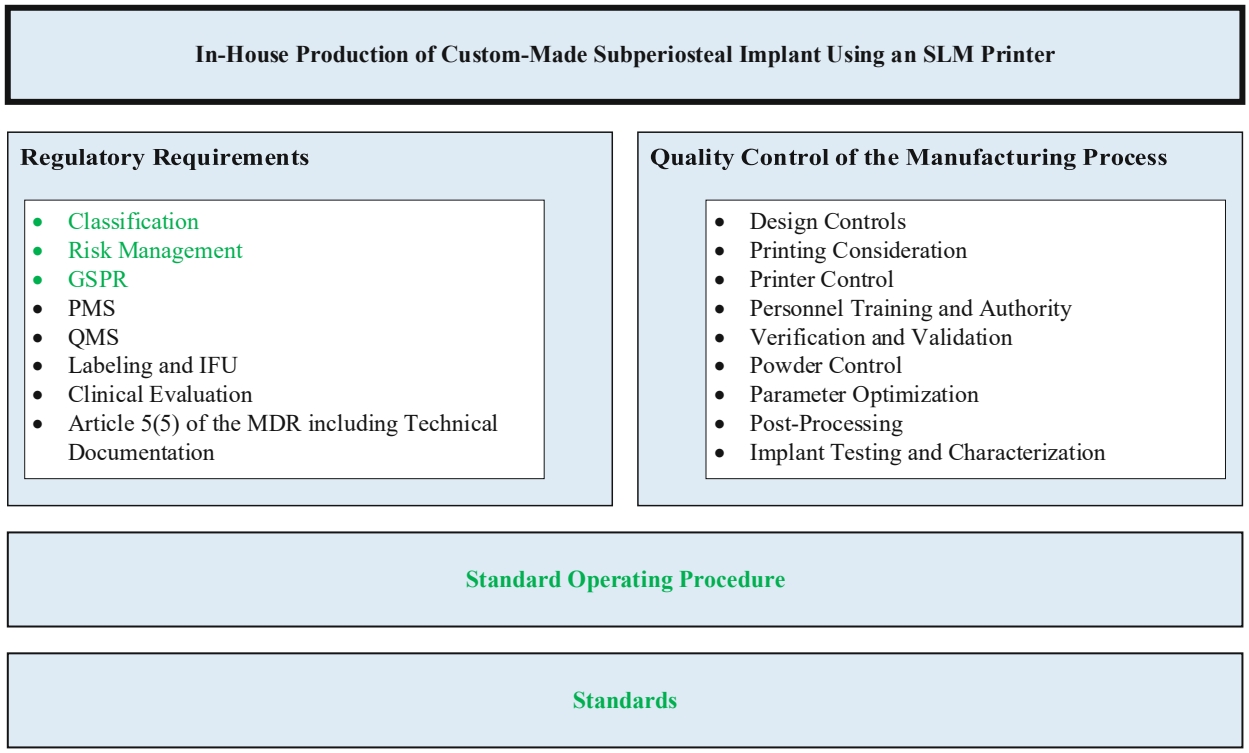

Figure 11: Regulatory requirements and quality assurance during the manufacturing of the CMSI. The green bullet points are realized in theory and practice, the black bullet points in theory.

4.1 Regulatory Requirements and Documents According to the Medical Device Regulation (EU 2017/745) for A Custom-Made 3D Printed Titanium Implant at the General Hospital of Vienna (AKH)

As discussed in section 3.1 of this thesis, the regulatory requirements are very important for the AM of the CMSI at the CMPBME. In this regard, documentation is essential to fulfill regulatory requirements and prove compliance with these regulatory requirements to the authorized unit in Austria (BASG). Therefore, the respective relevant documents to fulfill the regulatory requirements are created for the printed CMSI. These documents also refer to each other to fulfill all requirements. In practice, these documents are saved in a specific file with restricted access. Furthermore, the documentation control including version control of the created documents must be observed.

Since this thesis intends to provide a thorough but clear and concise understanding of the process of the AM of a CMSI and its regulatory framework, this thesis concentrates on the key regulatory documents in this regard, as elaborated on in chapter 3. These documents are the classification

document, the GSPR, and the risk management. In addition to these main documents, the following files must be considered to bring a CMSI to the patient:

- Documentation regarding the QMS within CMPBME
- PMS and vigilance
- Labelling and IFU
- Clinical evaluation
- Technical file document including:
    - Details on the manufacturing facility
    - The description of the manufacturing process
    - Details on design and performance data

Further details and the regulatory background of these documents and for the classification document, the GSPR document, and the risk management document are elaborated on in section 3.1. To provide a practical example along the process of AM the CMSI in the course of this thesis, the finalized version of these three main documents (the classification, the GSPR, and the risk management documents) for this specific practical example are, furthermore, produced and presented in the supplementary documentation [54]. Additional practical guidance and information on the regulatory documentation required for the AM of CMDs at the AKH – as the templates for the three main documents in the supplementary documentation [54] – is provided by the regulatory unit of the CMPBME.

4.1.1 The Classification Document

The first of the three main regulatory documents, namely the classification document, which was drafted during the AM of the CMSI in the course of this thesis, concentrates on the classification of the CMSI as discussed in detail in section 3.1.5 of this thesis. As such, this document *inter alia* refers to the duration of application, the type of medical device, the application of implementing rules, the classification rules (MDR, Annex VIII, Chapter III), and the classification results. Considering the intended use and the characteristics of the CMSI, the rules from annex VIII of the MDR are analyzed and each rule is checked for its applicability. Each of the rules refers to a specific classification and the highest applicable classification is adopted. According to the classification, the CMSI is a class IIb medical device [54].

Due to the length of the classification document, however, the result of the work on this document for the particular practical example at hand is presented separately in the supplementary documentation [54].

4.1.2 The GSPR Document - Annex I of the MDR

As discussed in section 4.2 of this thesis, the GSPR document lists every requirement from annex I of the MDR. In practice, each of these requirements is checked for its applicability in practice. In case a requirement from the GSPR document is applicable, the relevant standard for verification of conformity of that requirement and reference documents that show the conformity are named in the GSPR document. In this regard, the standards discussed in section 4.2 of this thesis are to be considered. Adhering to this procedure, the GSPR document for the practical example of this thesis (the additively manufactured CSMI) is drafted in the course of this thesis. The GSPR document indicates that for the printed CMSI, the main applicable requirements refer to risk management and the biological evaluation of that device. For those requirements, the standards ISO 14971:2019 [50] and ISO 10993-1:2018 [127] can be used for the verification of conformity. Due to the length of the finalized GSPR document, however, the result of this work is presented separately in the supplementary documentation [54].

4.1.3 The Risk Management Document

As discussed in section 3.1.4, risk management is required for an additively manufactured CMSI, such as the practical example at hand. Consequently, a risk management report must be created which includes risk identification, risk analysis, and risk control. In this regard, the standards ISO 14971:2019 and ISO/TR 24971:2020 must be considered. As with the classification document and the GSPR document, the risk management document for the practical example at hand (the additively manufactured CMSI) is drafted according to this procedure in the course of this thesis. In the context of risk management, every possible harm is defined. Furthermore, a risk analysis is done using the parameters, probability of occurrence of harm P, and the severity of that harm S. Moreover, for each harm, measures are defined to reduce the probability of occurrence P. The risk management report for the CMSI at hand, as established in the supplementary documentation [54], shows that the CMSI has no unacceptable risks after applying the suggested measures [54]. Once again, due to its length, the finalized version of the risk management document for the additively manufactured CMSI is presented separately in the supplementary documentation [54].

4.2 Relevant Standards for the 3D Printed Titanium Subperiosteal Implants

As mentioned in section 2.5 of this thesis, the lack of standards regarding AM is still a challenge for manufacturers of medical devices such as the CMSI. In practice, there are still gaps in this regard and several standards are still in the process of development according to the F42 committee [29].

To provide a thorough but clear and concise understanding of the regulatory requirements for the AM of a CMSI, the relevant standards in this regard are analyzed correspondingly in the course of this thesis. As discussed in section 2.4 of this thesis, some of these standards are harmonized according to the MDR and their fulfillment equals conformity with the requirements stipulated by the MDR. In practice, these standards are also used to fulfill the requirements stipulated in annex I of the MDR.

Based on a thorough analysis of the standardization framework for AM, this thesis compiles a list of the relevant standards for additively manufactured CMSIs (table 3) as a result of this analysis. It is important to highlight in this regard that these standards are selected for the AM with the SLM 125 printer at the CMPBME of a CMSI. Consequently, for other applications of the SLM 125 printer, other standards may apply. Since there are different standards in the field of AM of CMSI, this thesis categorizes the standards in table 3 according to general, design, material and product characterization, post-processing, and management standards. Furthermore, this thesis analyses whether the standards in question are harmonized and indicates the result accordingly in table 3:

Nr	**Standards**	**Harmonized**
	General	
1	EN ISO/ASTM 52900:2021 - General principles - Fundamentals and vocabulary	No
2	EN ISO/ASTM 52950:2021 - General principles - Overview of data processing	No
3	EN ISO/ASTM 52915:2020 - Specification for additive manufacturing file format (AMF) Version 1.2	No
4	ASTM F3001-14(2021) - Standard Specification for Additive Manufacturing Titanium-6 Aluminium-4 Vanadium ELI (Extra Low Interstital) with Powder Bed Fusion	No
5	ASTM 52930:2021 - Additive manufacturing - Qualification principles - Installation, operation and performance (IQ/OQ/PQ) of PBF-LB equipment	No

6	ASTM 52930:2021 - Additive manufacturing - Qualification principles - Installation, operation and performance (IQ/OQ/PQ) of PBF-LB equipment	No
7	ASTM F3456-22 - Standard Guide for Powder Reuse Schema in Powder Bed Fusion Processes for Medical Applications for Additive Manufacturing Feedstock Materials	No
8	EN ISO/ASTM 52921:2019 - Additive manufacturing - General principles - Standard practice for part positioning, coordinates and orientation	No
9	EN ISO/ASTM 52904:2022 - Additive Manufacturing – Process Characteristics and Performance - Metal powder bed fusion process to Meet Critical Applications	No
10	ASTM F2924-14 Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium with Powder Bed Fusion	No
11	ISO/AWI 5092 Additive manufacturing for medical - General principles - Roadmap to safe and effective additively manufactured implants	No
	Design	
12	EN ISO/ASTM 52910:2022 - Additive manufacturing - Design - Requirements, guidelines and recommendations	No
13	EN ISO/ASTM 52911-1:2019 Additive manufacturing - Design - Part 1: Laser-based powder bed fusion of metals	No
	Material and Product Characterization	
14	ASTM F3049 - 14 (2021) - Standard Guide for Characterizing Properties of Metal Powders Used for Additive Manufacturing Processes	No
15	ASTM F3571-22 - Standard Guide for Additive Manufacturing – Feedstock – Particle Shape Image Analysis by Optical Photography to Identify and Quantify the Agglomerates/Satellites in Metal Powder Feedstock	No
16	EN ISO/ASTM 52907:2020 - AM - Feedstock materials - Methods to characterize metal powder	No
17	ISO 20160:2006 - Implant for surgery - Metallic materials - Classification of microstructures for alpha+beta titanium alloy bars	No
18	ASTM F3335-20 Standard Guide for Assessing the Removal of Additive Manufacturing Residues in Medical Devices Fabricated by Powder Bed Fusion	No
	Post-Processing and Testing	
19	ASTM F2971 - 13 (2021) - Standard Practice for Reporting Data for Test Specimens Prepared by Additive Manufacturing	No
20	EN ISO/ASTM52909:22 Additive manufacturing of metals - Finished part properties - Orientation and location dependence of mechanical properties for metal powder bed fusion	No
21	ASTM F3122 - 14 (2022) - Standard Guide for Evaluating Mechanical Properties of Metal Materials Made via Additive Manufacturing Processes	No

22	ASTM F3301 - 18a - Standard for Additive Manufacturing - Post Processing Methods - Standard Specification for Thermal Post-Processing Metal Parts Made Via Powder Bed Fusion	No
23	ASTM F3302 - 18 - Standard for Additive Manufacturing - Finished Part Properties - Standard Specification for Titanium Alloys via Powder Bed Fusion	No
24	ASTM F3530 - 22 - Standard Guide for Additive Manufacturing - Design - Post-Processing for Metal PBF-LB	No
25	EN ISO/ASTM DIS 52908:2022 - Additive manufacturing of metals - Finished Part properties - Post-processing, inspection and testing of parts produced by powder bed fusion	No
26	ISO 17296-2:2015 Additive manufacturing—General principles—Part 2: Overview of process categories and feedstock	No
27	EN ISO 10993-1:2020 - Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	Yes
28	EN ISO/ASTM52902:2021 - Additive manufacturing - Test artifacts - Geometric capability assessment of additive manufacturing systems	No
29	ASTM E8/E8M - 15a - Standard Test Methods for Tension Testing of Metallic Materials	No
	Management	
30	EN ISO 13485:2016 - Medical Devices - Quality management system - Requirements for regulatory purposes	Yes
31	EN ISO 14971:2022 - Medical devices - Application of risk management to medical devices	Yes
32	ISO/TR 24971:2020 - Medical devices - Guidance on the application of ISO 14971	No
33	EN ISO 14155:2021 - Clinical investigation of medical devices for human subjects - Good clinical practive	No
34	ISO 9001:2015 Quality management systems - Requirements	No
35	ISO 12052:2017 Health informatics - Digital imaging and communication in medicine (DICOMI including workflow and data mangement	No
	Dental Implants	
36	EN 1642:2012 - Medical devices for dentistry - Dental implants	No
37	EN ISO 7405:2019 - Dentistry - Evaluation of biocompatibility of medical devices used in dentistry	No
38	EN 14630:2022 - Non-active surgical implants - General requirements	Yes
39	EN ISO 10451:2010 - Dentistry - Contents of technical file for dental implant systems	No

Table 3: Standards required for the AM of a CMSI

4.3 The Additively Manufactured Custom-Made Titanium Subperiosteal Implant (CMSI)

4.3.1 Design and Additive Manufacturing

As described in section 3.3.3 of this thesis, a CMSI is designed based on the anatomical structure and function of the Maxilla of an anonymized patient (figure 7) as an example for the regulatory procedure of CMDs. This subperiosteal implant is designed in Materialise and the STL model created in the course of this thesis can be seen in figure 12.

Figure 12: Design Subperiosteal implant for the printing in the SLM 125

Furthermore, the CMSI is placed on the anatomical model in Materialise. This can be seen in figures 13 and figure 14.

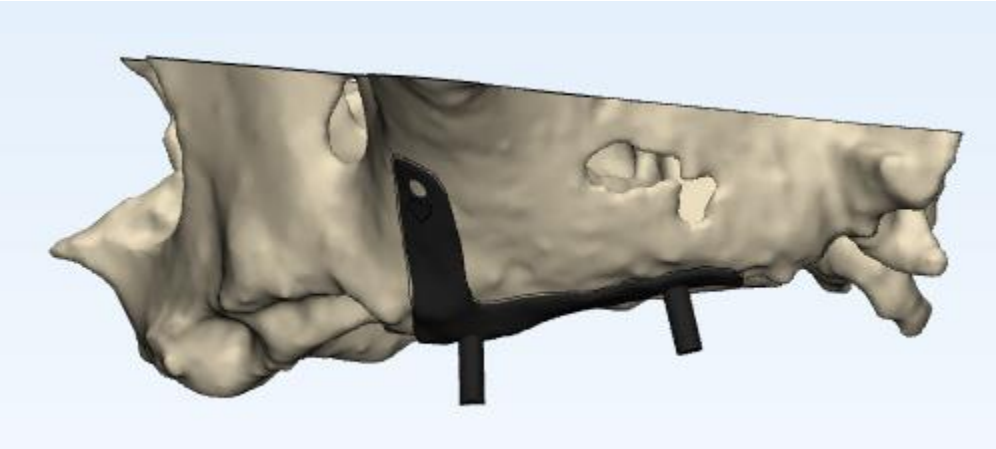

Figure 13: CMSI on the maxilla; left lateral view.

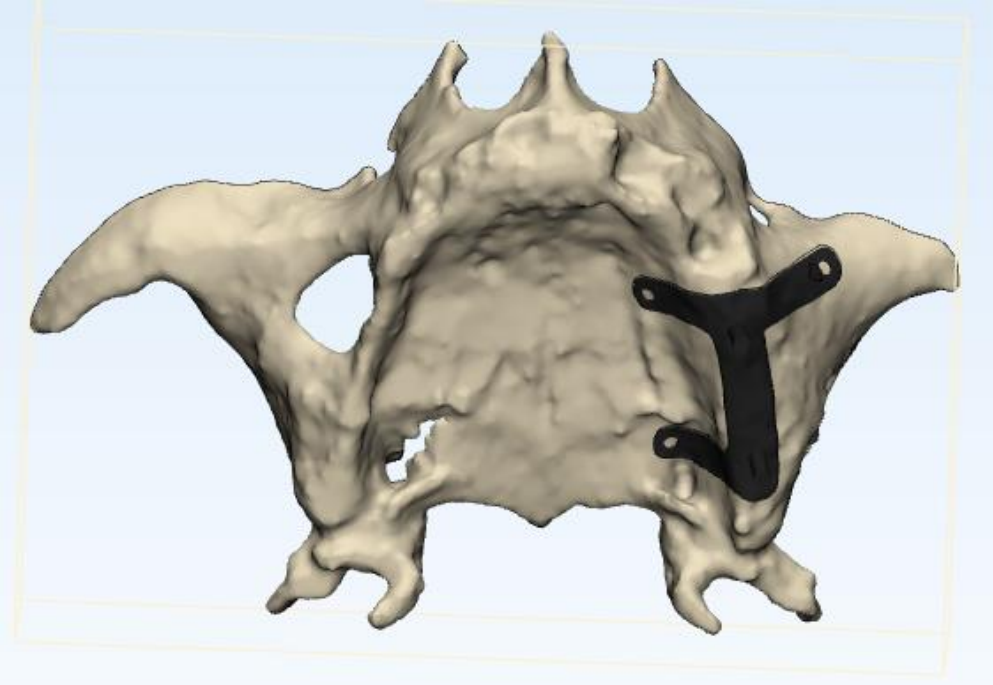

Figure 14: CMSI on the maxilla; Inferior view.

Figure 15 shows the as-built CMSIs with support structures on the base plate of the SLM 125 printer. Three CMSIs are printed in the course of this thesis as can be seen in figure 15. Additionally, two dog-bones are printed to be mechanically tested and compared to the specification from the data sheet of the powder in further projects [129].

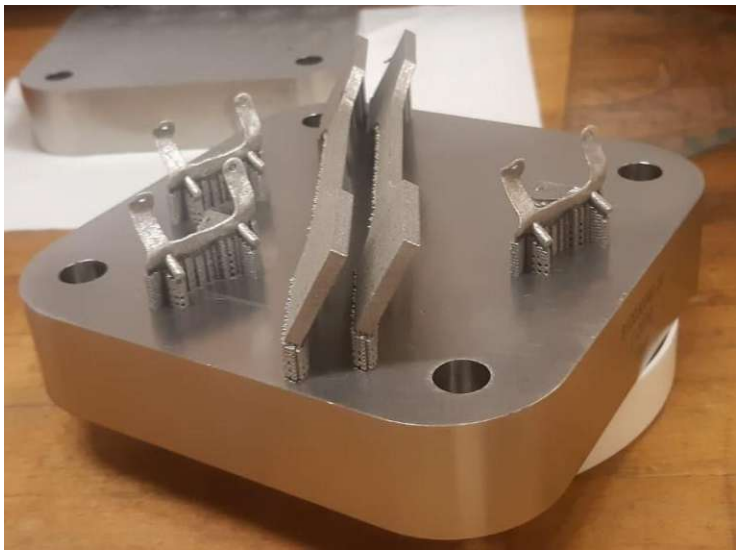

Figure 15: The printed CMSIs and dog-bone.

4.3.2 Material Characterization of the Cutom-Made Subperiosteal Implant (CMSI)

As mentioned in section 3.3.6, the 3D measurement system head (VR-5200) from the company Keyence can be used at the CMPBME to analyze the roughness of the CMSI. In order to do so, the as-built implant is scanned with the Keyence measurement system. With the corresponding software, between two points on the implant, 11 individual measuring sections are chosen, and the roughness is measured. Figure 16 (left) shows the line (in red) between these two points on the CMSI. On the right side of figure 16, the measured roughness along the red line (at 11 measuring sections) can be seen. The x-axes indicates the distance between the two points and the y-axes exhibit the roughness along the red line for 11 measuring segments (delimited by the vertical lines), both in µm. The calculation of the mean value of roughness for these 11 segments results in a roughness of 16.877 µm.

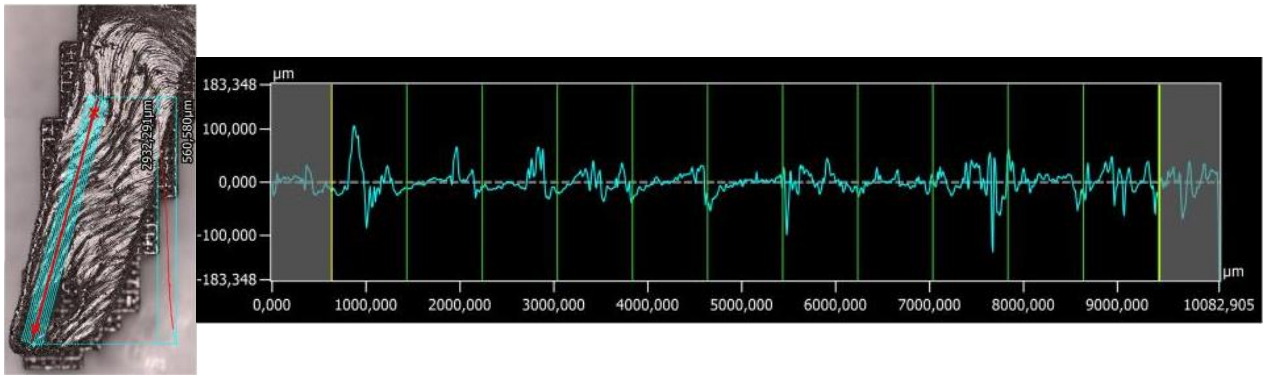

Figure 16: On the left side, the measuring sections along the red line on the CMSI can be seen. On the right side, the roughness along the red line (devided in 11 segments) can be seen.

4.4 Standard Operating Procedure for Custom-Made Titanium Implants within Vienna General Hospital

In the following, the Standard Operating Procedure (SOP) for the AM of medical devices with the SLM 125 printer at the CMPBME are established. This SOP is written considering the MDR requirements mentioned in sections 3.1 and 3.2, the process of AM of CMDs with the SLM 125 printer as discussed in section 3.3, and the findings regarding the SOP for additively manufactured medical devices as discussed in section 3.4. Furthermore, current relevant standards as elaborated on in section 4.2 are considered in the drafted SOP. Each step of the SOP refers to specific Work Instructions (WI) which should be provided by the person responsible on-site at the CMPBME for each respective step.

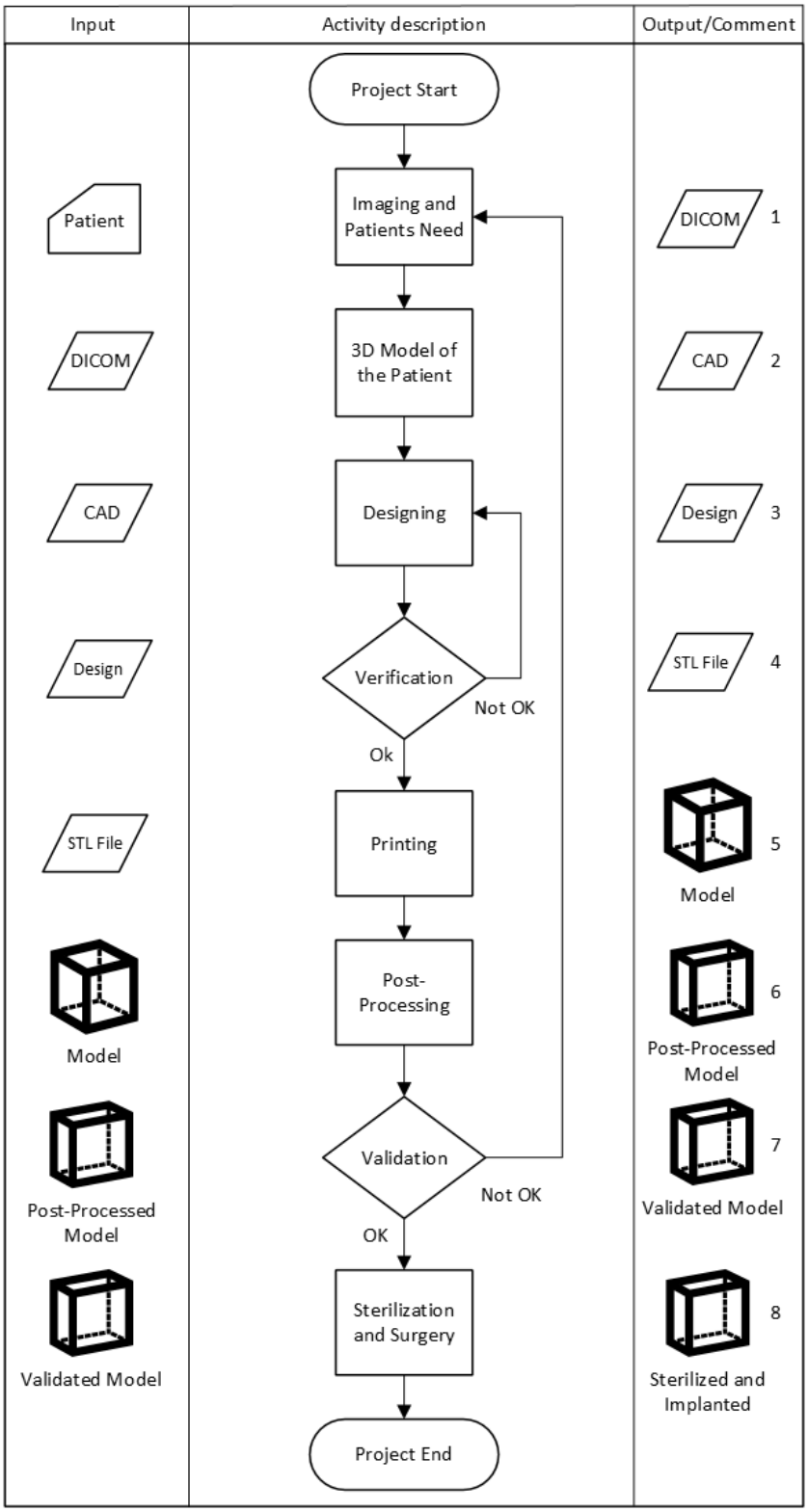

Figure 17: Standard operation procedure for CMDs with the SLM 125 printer at the CMPBME.

1) The first meeting with the surgeon and the manufacturing must be organized. At this meeting the patient needs and the manufacturing process and timelines must be defined and discussed. A patient file must be created and made accessible for relevant sides.

   Current images (CT, MRI, etc.) from the patient with their needs must be saved in the patient file considering the standard ISO 12052:2017. In this stage of the process, the MDR requirements must be considered. In this regard, the following documents must be created and considered for the rest of the process: The classification including the intended use, the GSPR, and risk management.

2) The DICOM information of the patient is used to print an anatomical model of the concerned area of the patient. This step must be discussed in another sub-process, which consists of the modeling, the printing method, the used material, and the validations with different WIs. At the end of this process, a CAD model is established.

3) The anatomical model of the patient is used to design a customized medical device (e.g.: an implant). In this regard, relevant standards (e.g.: EN ISO/ASTM 52910:2022, EN ISO/ASTM 52911-1:2019) must be considered. A WI for modeling the medical device and the auxiliary tools at the CMPBME must be considered.

4) Model verification is performed by virtually fitting the designed medical device over the 3D model of the patient. Furthermore, FEM can be done to improve the mechanical properties of the designed medical device. The output of the procedure must be a new design with a new version number. This procedure is repeated until the designed medical device fits best to the patient's anatomical structure and function. The surgeon has to review every version of the design and these versions must be saved in the patient file. After the Model is verified, it is converted into an stl file for the next step.

5) After the verification of the design of the medical device, the printing procedure starts. The input of the procedure is an STL file and the output is a customized 3D titanium medical device. In this process, the following sub-procedures must be considered: The procedure for parameter optimization, the procedure for maintenance of the SLM 125 printer with all the hazard considerations, the procedure for quality control of the powder, the procedure for waste handling, the procedure for printing with its safety considerations, and the procedure for personnel training and equipment. During the printing, the Melt Pool Monitoring (MPM) and the Laser Power Monitoring (LPM) systems to analyze the printing should be used. Furthermore, the following WIs must be available at the corresponding work area on-site: Printing and safety considerations (including before printing, during printing, and after printing), cleaning of the printer, sieving of the powder, and powder analysis).

6) The printed implant (as-built) needs to be post-processed depending on the application. For titanium implants, the following post-processing steps are suggested: Hot Isostatic Pressing (HIP), Sandblasting (SB), and Chemical Etching (CE). Relevant standards from the ASTM F42 committee should be observed. For each of these post-processing steps, a WI must be available on-site.

7) The post-processed medical device needs to be validated to ensure that quality requirements are met. The surface properties and material properties of the printed medical device are characterized. For surface characterization, the following imaging techniques can be used: Scanning Electron Microscopy (SEM) and the Wide-Area 3D Measurement System. The latter is also used for shape derivation inspection of the printed medical device. To test the mechanical properties of the device, either software-based testing such as FEM or a tensile testing device can be used. For the latter, the bounding conditions of the device under test must be observed. For these characterizations, relevant WIs must be available on-site. Clinical, mechanical, and biomaterial validation must be ensured in this step. If the validation is not reasonable, the process must start over from step 2) of the SOP, the patient needs.

8) After the validation and depending on the printed medical device, sterilization needs to be performed. At AKH, this is an internal process and the surgeon picks up the sterilized medical device from the sterilization unit for the surgery.

After the surgery, post-market surveillance (PMS) needs to be set up according to ISO 13485:2016. Reports for class I devices must be updated if necessary [11]. For class IIa, IIb, and III devices, a periodic safety update report (PSUR) according to article 86 of MDR must be prepared. For class IIb and III devices, this report must be updated at least annually. All the documents must be kept for 15 years.

5 Discussion

This diploma thesis deals with custom-made titanium implants that are additively manufactured and considers the regulatory challenges according to the MDR (regulation (EU) 2017/745) and the state of the art of this technology. In this regard, all the regulatory requirements for CMDs manufactured within a health institution are listed and discussed in accordance with the MDR and the MPG. To present a practical example of CMDs manufactured at the CMPBME, which is located at the general hospital of Vienna, the hands-on example of a CMSI is provided. This CMSI is printed with the SLM 125 printer at the CMPBME. Along with the process of manufacturing the CMSI, relevant regulatory documents and standards are presented, categorized, and discussed in this thesis. Furthermore, an SOP is established for future AM projects at the CMPBME to raise awareness for relevant regulatory requirements and quality assurance according to the new MDR.

The new MDR for medical devices provides stricter regulation for medical devices in the EU with additional 100 articles and 5 new annexes, compared to the previous MDD [1]. Additionally, the new Austrian MPG regulates the details of the MDR in Austria [2]. Studying the new MDR and the Austrian MPG, the term CMD stands out as a type of medical device. Understanding the definition of CMDs remains an ongoing issue that is discussed in numerous publications such as the MDCG 2021-3 document [3]. In this regard, the term “mass-produced” is not defined yet and thus remains a problematic term for manufacturers of CMDs in practice [137]. For the CMSI presented in this thesis, the definition of CMDs, nonetheless, applies.

An additional aspect that needs to be considered concerning additively manufactured medical devices is the lack of an official document provided by the European Commission in this regard, as established in the literature review of this diploma thesis. Therefore, documents from other authorities, such as the United States Food and Drug Administration, are considered to understand the quality control of additively manufactured medical devices.

Another ongoing issue for additively manufactured CMDs is the shortage of specific (harmonized) standards. However, the organizations for standards ISO and ASTM have established specific committees in this regard and are in the process of drafting additional relevant standards [32]. A list of the few standards which are currently available is provided in section 4.2 of this thesis.

Moreover, this diploma thesis lists and discusses the challenging regulatory requirements for CMDs. On this matter, an extensive literature review shows that literature on the regulatory requirements stipulated by the MDR for CMDs is scarce. Nevertheless, all regulatory requirements established by the MDR for CMDs are listed in section 3.1 of this thesis and must be observed in the manufacturing of any kind of CMDs. These requirements not only relate to the manufactured CMD itself but also to the management of the manufacturer and its facilities. For example, the CMPBME at the general hospital of Vienna is certified according to the standard ISO 9001. For manufacturing medical devices, several quality requirements in addition to ISO 9001 are needed according to the MDR, which are covered by the harmonized ISO 13485. Thus, additional quality requirements must be fulfilled at CMPBME to manufacture medical devices.

Furthermore, article 5 (5) of the MDR must be taken into account with regard to in-house devices. This article states that – except for the GSPR and the clinical evaluation – the regulatory requirements of the MDR do not apply to medical devices manufactured and used only within a health institution. These devices are also called in-house devices according to the MPG [2]. As a result, the regulatory requirements are lower for in-house medical devices such as the additively manufactured CMSI, as discussed in section 3.2 of this thesis. For the CMSI manufactured in the course of this thesis, the most relevant regulatory documents in this regard are created and compiled in the supplementary documentation [54]. These documents are the classification document, the GSPR, and the risk management report. These regulatory documents are not only required by the MDR and the Austrian authorized unit (BASG) but also help the manufacturer to analyze their produced medical device with regard to quality, effectiveness, risk reduction, and overall improvement.

The CMSI, which is manufactured with the SLM 125 printer in the course of this thesis, represents a preliminary experimental basis for this thesis. Therefore, general instructions on the AM and the used SLM technique, the material, and the printer are discussed in section 3.3. Additionally, the CMSI at hand for patients with severe bone atrophy is introduced and the anatomical model, from

which the CMSI is designed and manufactured in the course of this thesis, is presented. For the design process of the CMSI, relevant standards such as the ISO/ASTM 52911-1:2020 and ISO/ASTM 52910:2020 are considered [108, 109]. These standards also contain warnings that need to be taken into account for the design process. However, a lack of standards for the design process regarding the anatomical, biological, functional, and aesthetic requirements is noticed at this point of this thesis. However, the works from S. Barone et al. [110] and A. Surovas [111] are used to design a suitable CMSI. It is important to notice that every step of the design process must be reviewed and verified by the surgeon.

During the manufacturing process, the IFU of the printer, parameter optimization, and real-time process monitoring must be considered to reduce flaws in the implant. As can be seen in section 4.3 (figures 15 and 16), the printed CMSI is very rough. Thus, different post-processing steps, such as HIP and SB need to be considered for the printed implant. It remains important, however, that the final implant is objectively validated to meet the intended use and patient needs and is safe for the patient and any third party. This objective validation is usually performed by external vendors which test the manufactured device according to standards established in the GSPR document (such as ISO 10993-1:2018) and consequently provide the manufacturer with a test report. Since the AKH is equipped with a number of the respective test facilities, certain tests, such as the tensile test, can be performed at the AKH.

Based on the above considerations, this thesis shows that applying the same design, manufacturing, and quality control activities, as well as the same standards for additively manufactured medical devices repeatedly results in a controlled output and constant manufacturing process of medical devices [7]. Therefore, an SOP with state-of-the-art standards is established in this diploma thesis for future AM projects at the CMPBME. The established SOP considers the design process, the manufacturing, the maintenance of the printer and powder, the characterization and post-processing steps, the regulatory requirements from the MDR, and the verification and validation of the final version of the printed implant. Considering future projects at the CMPBME in this regard, the presented SOP can be improved and adjusted more precisely to regulatory requirements and the equipment available at the CMPBME after multiple runs for different projects. In table 1, the main steps of the SOP are listed.

Steps	Activity
1	Imaging and patient needs
2	3D model of the patient
3	Designing
4	Verification
5	Printing
6	Post-processing
7	Validation
8	Sterilization and surgery

Tabe 4: Main steps of the SOP

While this study provides valuable insights into the requirements of CMDs within a health institution and their quality control, certain limitations must be acknowledged. As the MDR is a new regulation, the practical implementation of its requirements is still in its early stages and details on its implementation are still to be determined by institutions such as the MDCG. In addition, academic literature and research in this field are recent and thus limited. Furthermore, due to the lack of guidelines for AM of medical devices from the European Commission, guidelines from the FDA (U.S.) are used to establish a quality control process for the manufacturing of the CMSI in the course of this thesis. Moreover, this thesis does not involve a physician in the design process of the CMSI (including validation and verification) and the risk management processes. This is, however, due to the fact that no patient is involved in this thesis and the CMSI is thus solely serving as an example. Nonetheless, it has to be pointed out in this regard that the involvement of a patient and thus a physician would go beyond the scope of a diploma thesis.

Before concluding this thesis it must, however, be mentioned that an additional relevant MDCG (MDCG 2023-1) on in-house productions has been published in January 2023 and thus subsequent to the finalization of this diploma thesis. While this thesis considers the relevant literature, regulations, standards, and guidelines at the time of its writing (status quo 2022), the MDCG 2023-1 is thus not considered. In brief, the MDCG 2023-1 contains additional information on in-house production and CMDs and must thus be taken into account during future projects relating to the in-house manufacturing of CMDs at the CMPBME [138]. This shows, however, the nature of the legal framework as a constantly evolving and thus changing system. Consequently, each new

project requires state-of-the-art research on relevant standards and a thorough review of these standards to be up to date and to comply with the latest regulatory framework.

6 Conclusion

This diploma thesis elaborates on additively manufactured custom-made titanium implants and takes the state of the art of this technology and the related challenges and requirements according to the MDR (EU) 2017/745 into account.

The MDR introduces new possibilities for health institutions such as the AKH to manufacture CMDs. Therefore, this thesis establishes a general understanding of the regulatory requirements for the manufacturer of CMDs and the manufacturer of in-house devices in accordance with the MDR and the Austrian MPG. This allows the CMPBME, which is located in AKH, to manufacture CMDs and put them into service within the AKH. To fulfill the requirements stipulated by the MDR, numerous regulatory documents must be generated. The three most relevant documents in this regard are created and compiled in the supplementary documentation, which is based on this thesis, and should serve as an example for future projects [54].

Furthermore, this thesis presents, categorizes, and discusses standards relevant to the manufacturing of safe CMDs according to the state-of-the-art of technology, in particular the standards provided by ISO and ASTM. The set of standards is, however, not complete yet, since additional standards are currently developed by the responsible committees from the ISO and ASTM organizations. This and the constantly improving and thus changing legal framework show that each new project requires state-of-the-art research on relevant standards and a thorough review of these standards to be up to date and to comply with the latest regulatory framework.

Another achievement of this thesis is the creation of an SOP for manufacturing CMDs with the SLM 125 printer at the CMPBME. This SOP describes the process of manufacturing CMDs with the SLM 125 printer and provides information and relevant standards for each step of this process.

As discussed in this thesis, the CMPBME can perform as a manufacturer of CMDs according to the MDR. This thesis intends to serve as the groundwork for the AM of CMDs at the CMPBME by providing an overview and practice-oriented categorization of the regulatory requirements, in particular the MDR and the MPG, as well as the relevant standards from ISO and ASTM, and by establishing an SOP for the AM of medical devices with the SLM 125 printer at the CMPBME. It

shall thus serve as a guideline for future projects to manufacture safe and controlled medical devices in accordance with the relevant legal framework.

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