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Regulations concerning additive manufacturing

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Regulations concerning additive manufacturing

This thesis delves into the principles of 3D printing and the oversight of medical device regulations across Europe, the USA, and other global regions. It explores how regulatory bodies classify regulations and identifies commonalities between these classifications. The focus lies on reviewing current regulations governing 3D printed medical devices and forecasting future regulatory changes.
Observations indicate a trend toward harmonizing regulations, particularly evident in the evolving regulations of the EU. Forecasts envision simplified and standardized regulations globally, aimed at enhancing patient safety. The anticipation underscores the importance of registering new and updated medical devices well in advance across diverse global regions.

This thesis contains the changing regulations in the EU and the US for 3D printed medical devices, considering newer technologies, and emphasizing standards for safety. Used manufacturing materials, drugs, and personalization of devices influence risk classifications, while the implementation of Universal Device Identification (UDI) aims to improve traceability and surveillance.

Keywords:

3D printing, medical devices, regulations, anticipation, future regulations.

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Lisäävän valmistuksen regulaatiot

Tämä opinnäytetyö syventyy 3D-tulostuksen periaatteisiin ja lääkinnällisten laitteiden säätelyn valvontaan Euroopassa, Yhdysvalloissa ja muualla maailmassa. Työssä selvitetään regulaatioelinten luokittelevat säädökset ja tunnistetaan yhtäläisyyksiä näiden luokittelujen välillä. Painopiste on nykyisten 3D-tulostettujen lääkinnällisten laitteiden regulaatioiden tarkastelussa ja tulevien regulaatiomuutosten ennustamisessa. Havainnot osoittavat trendin kohti regulaatioiden harmonisointia, erityisesti EU:n kehittyvissä regulaatiomuutoksessa. Ennusteet viittaavat globaaliin yhtenäistyvien regulaatioiden trendiin, joilla pyritään parantamaan potilasturvallisuutta. Tämä ennuste korostaa päivitettyjen lääkinnällisten laitteiden aikaisen rekisteröinnin tärkeyttä.

Opinnäytetyö käsittelee regulaatiot EU:ssa ja Yhdysvalloissa, koskien 3D-tulostettuja lääkinnällisiä laitteita ottaen huomioon uudet kehittyvät teknologiat ja niihin liittyvät turvallisuusregulaatiot. Laitteiden valmistusmateriaalit ja laitteiden personointi vaikuttavat selvästi riskiluokituksiin. Samalla yksilöllinen laitetunniste (UDI) pyrkii parantamaan laitteiden jäljitettävyyttä.

Asiasanat:

3D tulostus, lääkinnällinen laite, regulaatiot, ennuste, tulevat regulaatiot.

Content

Figures

Tables

List of abbreviations

AMBioPharma	Centre for Additive Manufacturing for Life Science and Pharmaceutical Industry
AMDC	ASEAN Medical Device Committee
AMDD	ASEAN Medical Device Directive
ANMAT	Argentina’s National Administration of Drugs, Foods, and Medical Devices
ANVISA	Brazilian Health Regulatory Agency
APEC	Asia-Pacific Economic Cooperation
ASEAN	Association of South Asian Nations
ASTM	American Society for Testing and Materials
CDS	Clinical Decision Support
CDSCO	India’s Central Drugs Standard Control Organization
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practices
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices
FDA	Food and Drug Administration

FDM	Fused Deposition Modeling Printing
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practices
HSA	Singapore’s Health Sciences Authority
IMDRF	Medical Device Regulators
INVIMA	Colombia’s National Institute for Food and Drug Surveillance
INVIMA	Colombia’s National Institute for Food and Drug Surveillance
IP	Intellectual Property
ISO	International Organization for Standardization
ISP	Chile’s Institute of Public Health
IVD	In Vitro diagnostic
IVDD	In Vitro diagnostic medical devices
IVDR	In Vitro Diagnostic Medical Devices Regulation
JMDN	The Japan Medical Device Nomenclature
KFDA	Korea Food and Drug Administration
MDCG	Medical Device Coordination Group
MDD	Medical Devices Directive
MDEL	Medical Device Establishment License

MDL	Medical Device License
MDR	Medical Device Regulation
MDSAP	Medical Device Single Audit Program
MFDS	South Korea Ministry of Food and Drug Safety
MHLW	Japan Ministry of Health, Labor and Welfare
NMPA	China’s National Medical Products Administration
PMA	Premarket Approval
PMD Act	Japan Pharmaceuticals and Medical Devices Act
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
PMS	Post Market Surveillance
QMS	Quality Management System
QMS	Quality Management System
RHSC	Regulatory Harmonization Steering Committee
SaMD	Software as a Medical Device
SLA	Stereolithography Printing
SLS	Selective Laser Sintering Printing
TGA	Australia’s Therapeutic Goods Administration

TR	Technical Report
UDI	Unique Device Identification
WHO	Health Organization

1 Introduction

Additive manufacturing, often used interchangeably with 3D printing, constitutes a diverse range of layer-by-layer manufacturing processes for crafting three-dimensional objects. In the thesis, 3D printing primarily references this broader spectrum within additive manufacturing. This method involves creating a 3D digital model, subsequently translated into sliced designs read by the 3D printer. Printing the object layer by layer, potentially using supports for intricate structures. Post-processing like support removal, surface refinement, or painting may be necessary after printing. Various 3D printing technologies, such as Fused Deposition Modeling (FDM), Stereolithography (SLA), and Selective Laser Sintering (SLS), employ distinct methods like melting, curing, or binding materials to realize the intended design. There are many different methods with different ways of printing items in 3D, as explained before SLA or photopolymerization that uses resin with hardening light. SLS or powder bed fusion that fuses layers of powder together with lasers. binder jetting that uses liquid binding agent to bind powder layers together. FDM or directed energy deposition with material melted together in layers, and sheet lamination with binding thin sheets of low-temperature material together layer by layer and many new methods to come. (Matulka, R. 2014; 3D Printing Industry 2017.)

While 3D printing can be used in vast possible ways and it is exciting in how many ways it can be used, one of the newer implements for 3D printing is in medical device manufacturing and device testing. 3D printing can be a cheaper and faster way to manufacture different customized medical devices for patients and to test new ways of drug implementations, or even to manufacture instruments for medical use. (Azzouzi, M. 2018.) It is still quite a new way to manufacture different devices and as such it has been in some cases complicated to apply older medical device regulations for 3D printed medical devices. This is why regulations for medical devices will be updating in the years to come as seen in the new EU medical device regulation 2017/745

(MDR) and some updated standards, like ISO 14971: 2019 Medical devices and ISO/ASTM 52910:2021- Additive manufacturing Design Requirements, guidelines and recommendations (Regulation (EU) 2017/745 MDR; SFS-EN ISO/ASTM 52910; SFS-EN ISO 14971). These standards and regulations and others are meant to better implement regulations for regular and 3D printed medical devices and possibly unify different regulation base lines to make patient safety and device safety more universal and reliable. (Contardi, M. 2019; EMA n.d.b.)

The objective of this thesis is to study what regulations there are now concerning 3D printed medical devices and how they might be updated in the future, and to anticipate regulation needs in research and development for upcoming medical devices. This study is directed towards easy learning and giving a way to people studying or people new to regulations of 3D printed medical devices, the basics of related regulations and what to expect in this field. Materials and topic of anticipated 3D printed medical device regulations are from the time this thesis is made and can be subjected to changes, depending on the way regulations work out in the end. (Byrne, R. 2019.)

This thesis is done for the Centre for Additive Manufacturing for Life Science and Pharmaceutical Industry (project AMBioPharma). The main goals of AMBioPharma project are to improve and accelerate product development and increase 3D printing (or additive manufacturing) especially for new products. The aim is to increase the usage of 3D printing and new materials for research and development, especially in southwest Finland’s industry. As well as to increase cooperation between companies in different sectors with developing 3D printed equipment and components, with increasing knowledge of 3D printing and usable materials. The priority of the specialization project being in pharmaceuticals and biotechnology, with innovation as a key word. (Åbo Akademi University 2021.)

2 Medical device regulation bodies

The regulations for medical devices (including 3D printed medical devices) are different depending on the intended use. As in Europe they are regulated at a member state level with European Medicines Agency (EMA) involved in the process (EMA n.d.b). The United States have the Food and Drug Administration (FDA) and its sub bodies for medical device regulations (FDA 2020). EMA and FDA are the two largest regulating bodies for medical devices in the western market, having a considerable influence in the medical device scene. There also are regulatory bodies in Canada and South America's different nations of which this thesis will include Brazil, Argentina, Colombia and Chile as they are important key nations in medical devices in South America and members of the Mercosur coalition, making them good examples for medical device regulations. There are vast amount of regulation bodies around the world as every nation has some regulations of their own concerning drugs and medical devices and health care for people. However, in this thesis, we will be only studying the EU, U.S, Canada, Brazil, Argentina, Colombia, Chile, Japan, China, South Korea, Australia, Singapore, and India as they are the primary ones of interest from the studies point of view. (WHO 2022.)

Table 1 presents these countries, their regulation bodies for medical devices and risk classifications. There are some different risk classifications in different countries, but many of them have the same type of classification.

Country/area	Risk classification	Regulation body for medical devices
EU	IVDR Class A, B, C, D and MDR I, IIa, IIb, III	EMA
US	I, II, III	FDA
Canada	I, II, III, IV	Health Canada
Brazil	I, II, III, IV	ANVISA
Argentina	I, II, III, IV	ANMAT
Colombia	I, IIa, IIb, III	INVIMA
Chile	I, II, III, IV	ISP
Japan	*(GC)I, (SCC)II, (CC)II, (CHCC)III, (HCC)III, (HCC)IV	PMDA
China	I, II, III	NMPA
South Korea	I, II, III, IV	MFDS
Australia	I, IIa, IIb, III	TGA
Singapore	Class A, B, C, D	HSA
India	Class A, B, C, D	CDSCO

*General Class I, Specified Controlled Class II, Controlled Class II, Specified Highly Controlled Class III, Highly Controlled Class III, or Highly Controlled Class IV

Table 1. Risk classifications and regulation bodies (Vivek, D etc. 2019).

Europe has a quite unified regulation processes as the EU has harmonized laws and regulations regarding drugs and medical devices in its area (EMA n.d.b). The regulations in the EU use the Medical Devices Directive (MDD) with its requirements for technical data, testing and certification processes. this makes the regulation unification inside the EU legally binding and can even impose imported medical devices to meet certain standards to be marketed in the EU. (EMA 2020).

The MDD being from the year 1994 is being replaced with the newer EU Medical Device Regulation (MDR), which is meant to make manufactured and imported medical devices more risk assertive and making clearer requirements for risk assessments and classifications for medical devices. (Contardi, M. 2019.)

There are also initiatives trying to harmonize and unified basic regulations for drugs and medical devices from a more global or area specific perspective.

One of the initiatives is the Asia-Pacific Economic Cooperation (APEC), with the Regulatory Harmonization Steering Committee (RHSC) that undertakes projects to promote regulatory convergence and cooperation in medical devices across its member economies in the Asia-Pacific region. (APEC 2023.)

The Medical Device Single Audit Program (MDSAP), has Australia, Brazil, Canada, Japan and U.S. as members and observers from EU, UK and World Health Organization (WHO) as well as affiliate members Argentina, Israel, South Korea and Singapore. MDSAP allows for the recognition of a single audit for medical device manufacturers, which can be used to meet the requirements of multiple regulatory authorities around the globe, including some in Asia. (Inter-American Coalition n.d.)

The International Medical Device Regulators Forum (IMDRF) is a global organization that includes regulatory authorities from Asia and other parts of the world and aims to harmonize medical device regulations worldwide. It has developed various guidelines and recommendations to drive the point of harmonization. (IMDRF n.d.)

2.1 European regulations of medical devices

The European regulation body for medical devices (including 3D printed ones) is EMA with the mix of regulations of EU members at state level. EMA oversees the implementation and cooperation of EU regulations within EU countries, to have a more unified regulation base in the EU. Medical devices are divided into four risk classifications as per MDR article 51. The medical device classifications are class I for low risk, class IIa for low medium risk, class IIb for high medium risk and class III for high-risk medical devices. As seen in the Figure 1. the data requirements of medical devices also go up with the risk classifications. (EMA. n.d.b.)

In the EU, 3D printed medical devices are regulated under the MDR 2017/745, which replaced the previous MDD. The MDR sets out the regulatory requirements for the design, manufacture, and commercialization of medical devices, including those produced using 3D printing technology. (Regulation (EU) 2017/745 MDR.)

The EU is also implementing the In Vitro Diagnostic Medical Devices Regulation (IVDR), as a new regulatory framework that governs the development, manufacturing, and commercialization of In Vitro diagnostic medical devices (IVDs) within the EU (Hall, A & Payne, S. 2018). The IVDR was adopted in 2017 and replace the previous EU Directive on In Vitro diagnostic medical devices (IVDD) (IVD-regulation, (EU) 2017/746). It was designed to improve patient safety, enhance the reliability of diagnostic results, and address technological advancements in the field of IVDs. (EMA. n.d.b.)

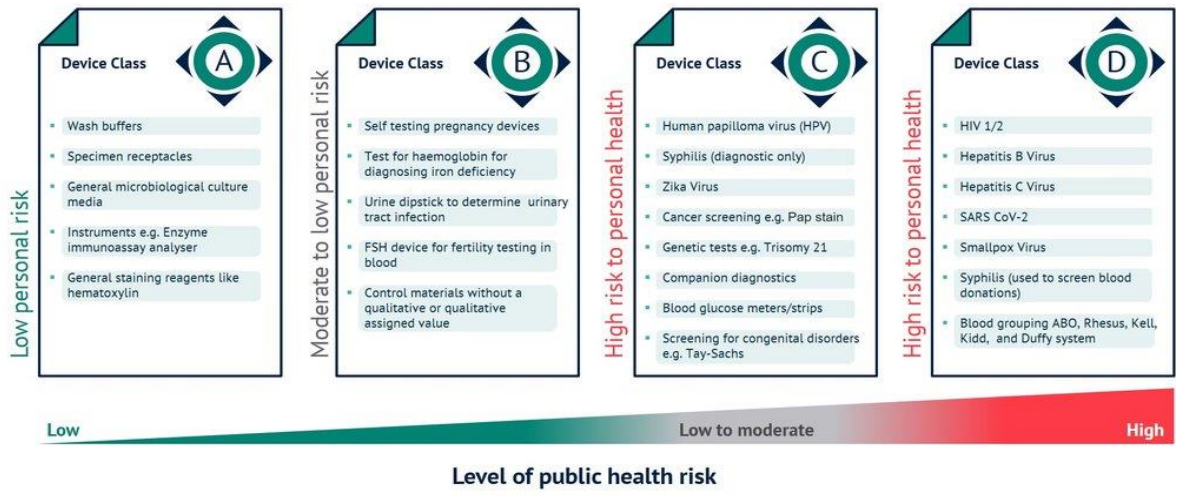

Figure 1. IVDR classifications (Mingay, H & Hendricusdottir, R. 2021).

The IVDR introduces another risk-based classification in tandem with the MDR system for IVDs (including those that are 3D printed). The classification is based on the potential risk posed by the devices to patients and users, and it determines the level of scrutiny and regulatory requirements that apply to each category of devices, as the IVDR classifies IVDs into four risk classes: Class A for Low risk, Class B for low to moderate risk, Class C for moderate to high risk,

and Class D for high risk, with Class D representing the highest risk category (Hall, A & Payne, S. 2018). This is shown in the Figure 1. with some examples for what kind of usages the IVDR risk classifications work.

Similar to the FDA's classification system, medical devices in the EU are categorized into different classes based on their risk level, where the classification determines the conformity assessment route that manufacturers of medical devices must follow. (Lundy, D. 2022).

Medical devices (including 3D printed devices) in the EU are required to undergo a conformity assessment procedure where the process includes activities such as quality management system certification, technical documentation review, and, in some cases, involvement of a notified body for higher-risk devices. (Byrne, R. 2019.)

Medical devices must have technical documentation that demonstrates the safety, performance, and compliance of the medical device with the essential requirements of the MDR, where the documentation includes details on the design, manufacturing process, materials used, and clinical evaluation. Clinical evaluation is also an essential component of the regulatory process for medical devices and 3D printed medical devices, as it involves gathering and assessing clinical data to demonstrate the safety and performance of the device with clinical evidence obtained from clinical investigations, scientific literature, and post-market surveillance data. (EMA. n.d.b.)

The MDR mandates the use of a Unique Device Identification system (UDI) for identifying and tracing medical devices throughout their lifecycle. This includes 3D printed medical devices, which must bear a UDI on their labeling to actively monitoring the devices safety and performance in usage. Manufacturers of 3D printed medical devices with the UDI must monitor their devices on the market and promptly report any incidents or adverse events to the competent authorities. (EMA. n.d.b.)

With the use of the UDI the MDR aims to enhance patient safety, improve transparency, and ensure the availability of safe and effective medical devices

within the EU market. This process places a greater emphasis on clinical evidence and post-market surveillance, to ensure ongoing device safety and performance evaluation.

As a note there are some global initiatives like the MDSAP and IMDRF that are trying to harmonize medical devices and drug regulations around the world to be more unified for patient safety, a bit like in the EU. (IMDRF Management Committee 2023; Inter-American Coalition n.d.)

2.2 North American regulations of medical devices

The North America consists of the Canadian and American regulations, in this thesis. While both regulatory authorities have similar goals of ensuring the safety and effectiveness of medical devices, there are variations in their specific requirements and processes. For instance, America has classifications from I - III and Canada from I – IV. (MaRS 2021.)

The regulatory framework in the United States medical devices (including 3D printed ones) are regulated under the FDA's framework, which includes the Food, Drug, and Cosmetic Act (FD&C Act) and the Code of Federal Regulations (CFR). In Canada, the regulation of medical devices (including 3D printed devices) fall under the Medical Devices Regulations as part of the Canadian Food and Drugs Act. (Health Canada 2022.)

2.2.1 United States

The regulation body for medical devices (including 3D printed ones) is the United States Food and Drug Administration (FDA), as they define medical devices with their Federal Food Drug and Cosmetic Act (FDC Act) and the FDA's regulatory framework for medical devices applies to all types of devices, including those produced using 3D printing technology. (FDA 2018.)

The FDA categorizes medical devices into three classes based on their level of risk to patients, and this classification determines the regulatory requirements and pathway for market authorization. The classifications are Class I for low-risk devices, Class II for intermediate-risk devices, and Class III for high-risk devices. (FDA 2018.)

The Class I and some Class II devices may be subjected to pre-market notification requirements as the device manufacturer must notify the FDA of the intent for the medical device. The FDA has 90 days to review the notification and determine if the device can be marketed. Class III and some Class II medical devices can be subjected to pre-market approval requirements, where the manufacturer must submit a detailed application to the FDA for review, including clinical data demonstrating the safety and effectiveness of the device. This is seen in Figure 2. (FDA 2018.)

Once a medical device is on the market, the FDA monitors its safety and effectiveness with post-market surveillances, when the medical device manufacturer is required to report to the FDA about any adverse events associated with the medical device. The FDA can order a recall of the medical device if necessary. (FDA 2018.)

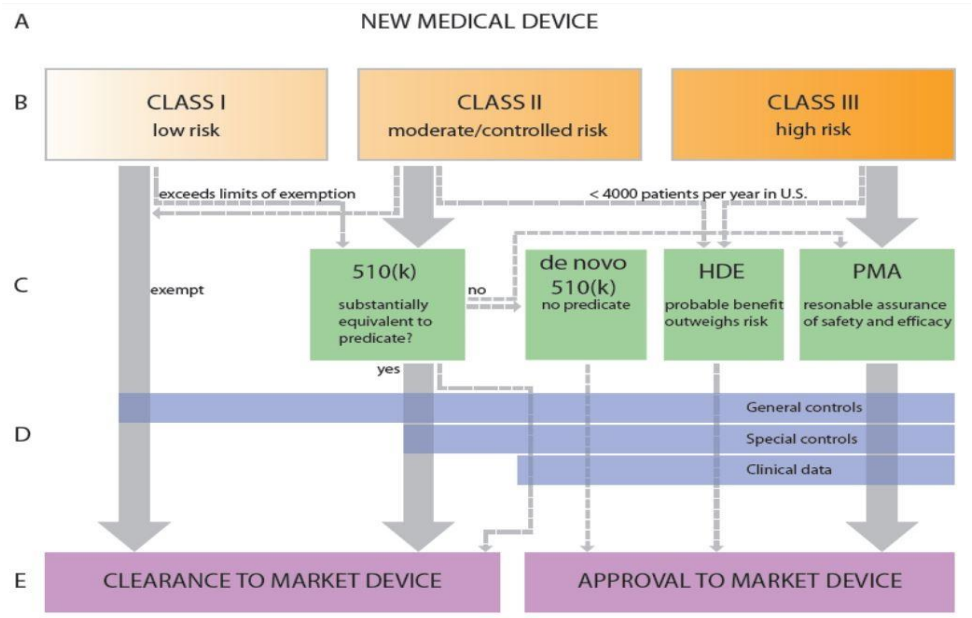

Figure 2. U.S. FDA Regulatory Process (Hoffmann, M.J. 2023).

Most low to moderate-risk 3D printed medical devices require premarket submission notification, known as a “510(k)” clearance, as seen on Figure 2. In the 510(k) clearance the manufacturer must demonstrate that the device is substantially equivalent to a legally marketed device in terms of safety and effectiveness (Wizemann, T. 2010). Whereas a high-risk 3D printed device that does not have a predicate device requires a Premarket Approval (PMA) application in which the manufacturer must provide comprehensive scientific evidence, including clinical data, to demonstrate the safety and effectiveness of the device. (FDA 2018.)

Manufacturers of medical devices must comply with the FDA's Quality System Regulation (QSR) under 21 CFR Part 820 and this regulation establishes requirements for quality management systems, design controls, process controls, and post-market surveillance. Manufacturers are also expected to adhere to the FDA's Current Good Manufacturing Practices (CGMP) to ensure the quality, safety, and consistency of their 3D printed medical devices where the CGMP includes requirements for design controls, production controls, labeling, and quality assurance. (FDA 2020.)

Medical device manufacturers are also required to establish a post-market surveillance system to monitor the safety and performance of their medical devices where they must report adverse events, device malfunctions, and other product-related issues to the FDA (FDA 2020). As seen on the Figure 2. where registration and device listing are needed for the medical device and manufacturer. The FDA has also implemented the UDI system, which requires certain medical devices, including 3D printed medical devices, to bear a unique identifier that helps facilitate device tracking, recalls, and post-market surveillance. (FDA 2020.)

Note that the specific regulatory requirements may vary based on the classification and intended use of the 3D printed medical device. Medical device manufacturers are encouraged to engage with the FDA early in the development process and consult relevant FDA guidance documents, for

detailed information specific to their device during the development. (FDA 2018.)

2.2.2 Canada

The regulation body for medical devices in Canada is Health Canada. And the regulatory requirements for 3D printed medical devices in Canada are primarily governed by the Medical Devices Regulations, as outlined in the Canadian Food and Drugs Act. (Health Canada 2022.)

Manufacturers of medical devices (including 3D printed devices) must hold a Medical Device Establishment License (MDEL) given by Health Canada. The MDEL demonstrates that the manufacturer meets the regulatory requirements for quality systems and device safety. The MDEL contains information of the licensed manufacturers, such as their license number, company name, address, company ID and authorized class of devices and licensed activities. (Health Canada 2023.)

Medical devices (Including 3D printed ones) are classified into different classes based on their intended use, duration of contact with the body, and potential risks. The risk classifications are Class I, Class II, Class III and Class IV, that are based on the risk assessment of the patient. Class I represents the least risky and Class IV the riskiest device, usually involving insertions. These categorizations can vary depending on what the medical device does. (Health Canada 2022.)

Higher-risk medical devices (usually Class III and IV), including some 3D printed devices, require a Medical Device License (MDL) from Health Canada before they can be marketed in Canada. The MDL application process involves providing evidence of safety, efficiency and quality compliance (Health Canada. 2022). For example, higher-risk (Class IV) 3D printed medical devices need clinical evidence demonstrating safety and effectiveness including clinical data from studies or clinical evaluation reports, especially for devices that are

substantially equivalent to existing devices or have novel characteristics. This is seen in Figure 3, as well as how the classifications compare with the U.S and EU. (MaRS 2021.)

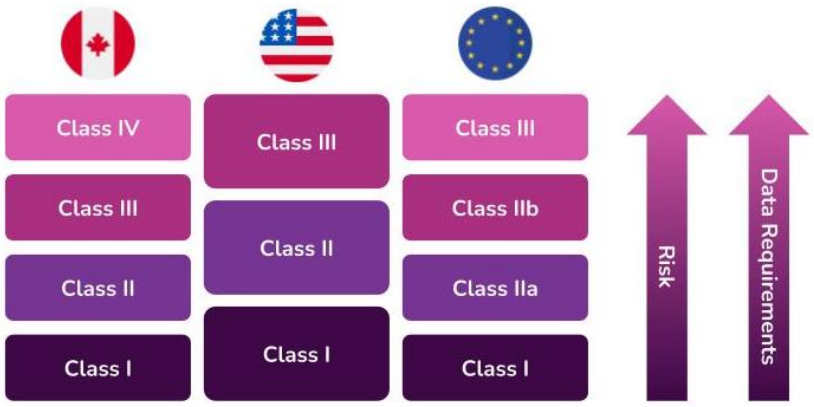

Figure 3. Medical Device classification comparison with Canada, U.S. and EU (Lundy, D. 2022).

2.3 South American regulations of medical devices

The Mercosur compromises of Argentina, Brazil, Paraguay, Uruguay as well as associated countries such as Bolivia, Chile, Colombia, Ecuador, Guyana, Peru and Suriname. The largest medical device market belonging to countries like Brazil and Argentina, having some influence in the continent. (Mercosur n.d.)

Medical device regulation in South America can be quite harmonized, as the South American trade associated Mercosur has unified several aspects of trade and regulations in areas like medical device regulations and imports. This gives a similar base for regulations on medical devices (including 3D printed ones) for the Mercosur countries, even though they are different countries with their own disposition. (Mercosur n.d.; MDRC 2023a.)

Some other notable global initiatives like the MDSAP and IMDRF, are also trying to harmonize medical devices and drug regulations in south America and globally. But in general, medical device regulatory requirements in Mercosur countries and associated countries are similar but not identical. The regulatory

procedures can be different in the same jurisdiction, with decisions for medical devices being made on a case-by-case basis. (Inter-American Coalition n.d.)

2.3.1 Brazil

The regulatory body for medical devices in Brazil is the Brazilian Health Regulatory Agency (ANVISA). ANVISA requires manufacturers of medical devices to register said medical devices (including 3D printed ones) before they can be marketed in Brazil. The registration process involves submitting technical documentation, including information on device safety, performance, and quality. (ANVISA n.d.)

ANVISA has four types of medical devices categories: medical equipment, materials for health use, orthopedic implants and In Vitro diagnostics. Medical devices have following risk classes: Class I for devices that have very low risk, Class II devices that have moderate risk, Class III devices that have an elevated risk potential and Class IV devices with considered critical risk. (ANVISA n.d.)

ANVISA oversees the regulatory requirements for 3D printed medical devices in Brazil. They are primarily governed by the medical device regulation RDC 185/2001 and regulation RDC 40/2015. (ANVISA n.d.)

3D printed medical devices are classified into different risk categories based on their intended use and potential risks to patients. The classification determines the regulatory requirements and conformity assessment procedures for market authorization. (ANVISA n.d.)

Medical device manufacturers are expected to establish and maintain a understandable Quality Management System (QMS) that complies with applicable standards and regulations, that should cover various aspects of device design, production, quality control, labeling, and post-market surveillance. This may involve conducting clinical studies or providing clinical data to support the medical device's performance. (Rocha, B etc. 2022.)

2.3.2 Argentina

The regulatory body for medical devices (including 3D printed ones) in Argentina is the National Administration of Drugs, Foods, and Medical Devices (ANMAT). The regulatory requirements for 3D printed medical devices in Argentina are primarily governed by regulation 311/2020. (Argentina.gob.ar n.d.)

Medical devices are classified into different risk categories based on their intended use and potential risks to patients. The classification determines the regulatory requirements and conformity assessment procedures for market authorization. The risk classes are from I to IV. (Regdesk 2019a.)

Medical device manufacturers of medical devices must obtain registration with ANMAT before they can be marketed and sold in Argentina. The registration process involves submitting technical documentation, including information on device design, materials, manufacturing processes, and evidence of safety and performance. (Regdesk 2019a.)

Medical device manufacturers are also expected to establish and maintain a Quality Management System (QMS) that complies with ANMAT applicable standards and regulations. The QMS should cover various areas of device design, production, quality control, labeling, and post-market surveillance. Depending on the risk classification, 3D printed medical devices may require a clinical evaluation to demonstrate their safety and effectiveness. This may insist on conducting clinical studies or providing clinical data to support the device's performance. (Argentina.gob.ar n.d.)

2.3.3 Colombia

The regulatory body for medical devices (including 3D printed devices) in Colombia is the National Institute for Food and Drug Surveillance (INVIMA). The regulatory requirements for 3D printed medical devices in Colombia are

primarily governed by regulation 2015166003, which establishes the technical requirements for the registration, control, and surveillance of medical devices. (EMERGO 2023f.)

Medical devices are classified by INVIMA into different risk categories based on their intended use and potential risks to patients, with risk classes I, IIa, IIb and III. The classification determines the regulatory requirements and conformity assessment procedures for market authorization. Medical devices must obtain registration with INVIMA before they can be marketed and sold in Colombia and the registration process involves submitting technical documentation, including information on device design, materials, manufacturing processes, and data of safety and performance. (Regdesk 2019c.)

Medical device manufacturers are expected to have and maintain a understandable Quality Management System (QMS) that complies with applicable standards and regulations, that also covers various areas of device design, production, quality control, labeling, and post-market surveillance. Depending on the risk classification, 3D printed medical devices may require a clinical evaluation to demonstrate their safety and effectiveness. This may involve conducting clinical studies or providing clinical data to support the device's performance. (EMERGO 2023f.)

2.3.4 Chile

The regulatory body for medical devices (including 3D printed devices) in Chile is the Institute of Public Health (ISP). The regulatory requirements for 3D printed medical devices in Chile are primarily governed by the Health Regulations for Medical Devices (Decreto Exento No. 3). (MDRC 2023b.)

Medical devices are classified into different risk categories based on their intended use and potential risks to patients. The classification determines the regulatory requirements and conformity assessment procedures for market authorization. The class is determined by the Supreme Decree that submits the

devices to regulation, and the classes are Class I: Devices that have very low risk, Class II: Devices that have moderate risk, Class III: Devices that have an elevated risk potential and Class IV: Devices considered critical risk. Depending on the risk classification, medical devices may need to undergo a conformity assessment process. (Regdesk n.d.) This process involves demonstrating compliance with relevant standards, safety, and performance requirements through various means, such as self-assessment or certification by a Conformity Assessment Body. With this the medical devices must obtain marketing authorization from the ISP before they can be legally marketed and sold in Chile. (MDRC 2023b.)

The authorization process involves submitting technical documentation, including information on device design, materials, manufacturing processes, and evidence of safety and performance. Medical devices are expected to establish and maintain a comprehensive Quality Management System (QMS) that complies with applicable standards and regulations, and the QMS should cover various aspects of device design, production, quality control, labeling, and post-market surveillance. (MDRC 2023b.)

2.4 Asian and Australia regulations of medical devices

The continent of Asia and its many nations can be more diverse in their regulations of drugs and medical devices, as they have their own regulatory authority and laws regarding medical devices. With different classifications, healthcare systems and cultures making it more difficult to share information and communication in this topic, even though some initiatives like the AMDD, APEC, MDSAP and IMDRF are trying to change that. (APACMed 2022.)

Asia has a more different or mix and match of regulations for medical devices for its many different countries and cultures have different views and opinions about medical usage and laws (Lamph, S. 2012). Some Asian countries have tried to uniform their endeavors by establishing and joining the Association of South Asian Nations (ASEAN) which has been a way to unify some of the drug

and medical device manufacturing and regulations. ASEAN has an ASEAN Medical Device Committee (AMDC) which is formed in 2014 to coordinate the ASEAN Medical Device Directive (AMDD) so the 10 member states could more easily facilitate medical device regulatory framework and reduce technical barriers within the ASEAN. (ASEAN 2015.)

The AMDD has the objective to harmonize and conform medical device regulations, trade and technical data documentation, with its member nations. The ASEAN ten country members are: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. With each member having their own national medical device regulatory body and unique regulatory medical device requirements. (ASEAN 2020.)

2.4.1 Japan

In Japan the regulatory body for medical devices (including 3D printed ones) is the Pharmaceuticals and Medical Devices Agency (PMDA) under the Ministry of Health, Labour and Welfare (MHLW). The regulatory requirements for 3D printed medical devices in Japan are primarily governed by the Pharmaceuticals and Medical Devices Act (PMD Act) and its associated regulations. (PMDA n.d.)

The PMD Act in Japan regulates medical devices and medical devices must obtain marketing approval from the PMDA before marketing and selling. The PMDA reviews medical devices technical documentation, conducts inspections, and evaluates the safety and effectiveness of the devices. The regulatory requirements for 3D printed medical devices in Japan are primarily governed by the PMD Act and its associated regulations. (PMDA n.d.)

The PMDA approval process for medical devices involves submitting technical documentation, including information on device design, materials, manufacturing processes, and preclinical and clinical data for reviving. For higher-risk 3D printed devices or other medical devices, clinical evaluation may be needed to demonstrate safety and effectiveness of the devices, and this

involves conducting clinical studies in accordance with GCP guidelines and providing relevant data to support the device's performance (Tamura, A. 2011). Medical device classifications in Japan are segmented into General Class I, Specified Controlled Class II, Controlled Class II, Specified Highly Controlled Class III, Highly Controlled Class III, or Highly Controlled Class IV (Regdesk. 2019b). For classification they use a coded predicate system combined with a rule-based risk assessment, based on the Global Harmonization Task Force (GHTF) classification rules. (Lamph, S. 2012.)

The Japan Medical Device Nomenclature (JMDN) give unique codes to identify the device classification and registration pathways given to the devices. JMDN also keeps a database of generic medical device descriptions. (PMDA n.d.)

Medical devices are expected to have and maintain a comprehensive Quality Management System (QMS) that complies with the ISO 13485, standard or its equivalent. The QMS should cover various aspects of device design, production, labeling, packaging, and post-market surveillance. (EMERGO 2023d.)

The PMDA has also implemented the UDI system in Japan, which requires certain medical devices, including 3D printed devices, to bear a unique identifier. This helps enhance traceability and post-market surveillance. (PMDA n.d.)

2.4.2 China

In China the regulatory body for medical device (including 3D printed ones) is the National Medical Products Administration (NMPA) and the requirements for registration and approval depend on the risk classification of the device. Low-risk devices can undergo self-assessment, while high-risk devices require technical reviews and clinical evaluations. Regulation for 3D printed medical devices is overseen by NMPA, formerly known as the China Food and Drug Administration (CFDA) and the regulatory requirements for 3D printed medical

devices in China are primarily governed by the Regulations for the Supervision and Administration of Medical Devices. (NMPA 2019.)

Medical device must obtain registration with the NMPA before they can be marketed and sold in China, with the registration process involving submitting technical documentation, including information on device design, materials, manufacturing processes, and preclinical and clinical data. Medical devices are classified into different categories by their potential risks to patients, with the classifications being Class I, II, and III based on their risk levels. Class I devices have the lowest risk, class II are the ones with moderate risk with technical management and control, and Class III includes those with the greatest risk requiring strict control. (Qserve 2023.)

Higher-risk medical devices may require clinical evaluation to demonstrate their safety and how they work, and this involves conducting clinical studies and providing clinical data in accordance with the relevant regulations and guidelines. Medical devices are expected to have and maintain a comprehensive QMS that complies with the ISO 13485 standard or its Chinese equivalent and the QMS should cover various aspects of device design, production, quality control, labeling, and post-market surveillance. (NMPA 2019.)

The UDI system is implemented by the NMPA in China, which requires certain medical devices, including 3D printed devices, to bear a unique identifier. This helps enhance traceability, post-market surveillance, and recalls if needed. The NMPA may require in some cases local testing of 3D printed medical devices conducted by designated testing institutions in China to ensure compliance with wanted safety and performance standards. (EMERGO 2023c.)

2.4.3 South Korea

The South Korean regulatory body for medical devices (including 3D printed ones) is the Ministry of Food and Drug Safety (MFDS) formerly known as the

Korea Food and Drug Administration (KFDA) that oversees the regulation of medical devices, and medical devices are subject to pre-market approval or notification processes based on their risk classification. As an important note to consider that some products classified as medical devices in the US or EU may be considered drugs or “quasi-drug” in South Korea. (MFDS n.d.)

The MFDS assesses the safety and efficacy of the devices before granting marketing approval. The classifications for medical devices in South Korea are Class I, Class II, Class III and Class IV, with Class I being with least risk and Class IV being the riskiest. (Regdeks 2020.)

The regulatory requirements for 3D printed medical devices in South Korea are primarily governed by the Medical Devices Act and its associated regulations. 3D printed medical devices must obtain registration with the MFDS before they can be marketed and sold in South Korea. The registration process involves submitting technical documentation, including information on device design, materials, manufacturing processes, and preclinical and clinical data. (MFDS n.d.)

Medical devices are expected to have and maintain a comprehensive Quality Management System (QMS) that complies with the ISO 13485 standard or its equivalent and the QMS should cover various aspects of device design, production, quality control, labeling, and post-market surveillance. The MFDS has also implemented the UDI system in South Korea, which requires certain medical devices, including 3D printed devices, to bear a unique identifier that helps enhance traceability, post-market surveillance, and possible recalls. (EMERGO 2023e.)

2.4.4 Australia

The Australian regulatory body for medical devices (including 3D printed ones) is the Therapeutic Goods Administration (TGA) which operates under the Australian Department of Health, and the level of regulatory framework depends

on the risk classification, ranging from self-assessment for low-risk devices to mandatory audits and approvals for high-risk devices. The regulatory requirements for 3D printed medical devices in Australia are primarily governed by the Therapeutic Goods Act 1989 and the Therapeutic Goods (Medical Devices) Regulations 2002. (TGA 2023a.)

Medical devices are classified into different risk categories based on their intended use and potential risks to patients. The classification determines the regulatory requirements and conformity assessment procedures for market authorization, with the classifications being Class I, Class IIa, Class IIb and Class III. With Australian classification rules being almost identical to the EU classification criteria, so classification in Australia will generally follow that of the EU. Depending on the classification, 3D printed medical devices may need to go under a conformity assessment process. That process involves demonstrating compliance with relevant standards, safety, and performance requirements through various ways, such as self-assessment, certification by a Conformity Assessment Body, or application for inclusion on the Australian Register of Therapeutic Goods (ARTG). (TGA 2023a.)

TGA's Essential Principles set out the fundamental requirements for the safety and performance of medical devices (including 3D printed ones), that must demonstrate conformity with these principles through appropriate evidence, such as design documentation, risk management plans, and clinical data. Medical devices are expected to have and maintain a comprehensive Quality Management System (QMS) that complies with the ISO 13485 standard or an equivalent quality management standard. The QMS should have various aspects of device design, production, quality control, labeling, and post-market surveillance. (TGA 2023b.)

TGA has also implemented the UDI system, which requires certain medical devices to bear a unique identifier. That will enhance traceability, post-market surveillance, and possible recalls. (TGA 2023b.)

2.4.5 Singapore

The Singapore regulation body for medical devices (including 3D printed ones) is the Health Sciences Authority (HSA). Medical device manufacturers must obtain the appropriate market authorization with the HAS, based on the risk classification of the device. Different risk categories for medical devices are based on the intended use and potential risks to patients. (HAS 2020.)

The HSA reviews technical documentation, conducts inspections, and assesses the safety and performance of the devices. The IVD classifications in Singapore are Class A for low individual risk and low public health risk, Class B for moderate individual risk and/or low public health risk, Class C for high individual risk and/or moderate public health risk and Class D for high individual risk and high public health risk. (EMERGO 2023b.)

Requirements for 3D printed medical devices in Singapore are primarily governed by the Health Products Act (HPA), and its associated regulations. Medical devices may need to go under a conformity assessment process, which involves demonstrating compliance with relevant standards, safety, and performance requirements through various means, such as self-assessment, certification by a Conformity Assessment Body, or application for inclusion on the Singapore Medical Device Register. Medical devices must gain registration with the HSA before they can be marketed and sold in Singapore. The registration process involves submitting technical documentation, including information on device design, materials, manufacturing processes, and evidence of safety and performance. (HAS 2020.)

Medical devices are expected to have and maintain a comprehensive QMS that complies with the ISO 13485 standard, or an equivalent quality management standard. The QMS should cover various aspects of device design, production, quality control, labeling, and post-market surveillance. (HAS 2020.)

2.4.6 India

In India the regulation body for medical devices (including 3D printed ones), is overseen by the Central Drugs Standard Control Organization (CDSCO), which operates under the authority of the Ministry of Health and Family Welfare. (CDSCO 2023.)

The regulatory framework for India medical devices is primarily governed by the Medical Devices Rules, 2017, under the Drugs and Cosmetics Act, where the CDSCO has established a risk-based classification system for medical devices in India, where the classification ranges from Class A (low risk) to Class D (high risk). The risk classification system determines the regulatory requirements and conformity assessment routes for medical devices. Where the medical devices are required to obtain the necessary approvals and registrations from the CDSCO, with the registration process involving the applying of required documentation, including technical specifications, manufacturing information, and proof of safety and efficacy. (Asia Actual n.d.)

The CDSCO may require conformity assessment for certain risk classes of medical devices, including higher-risk devices. Where the assessment is conducted by a notified body or a competent authority to evaluate the safety of the medical device. (CDSCO 2023.)

Medical devices are expected to have a robust QMS compliant with ISO 13485 or an equivalent standard, that can cover aspects such as design control, risk management, production processes, labeling, and post-market surveillance. (CDSCO 2023.)

3 3D printed medical device regulations

Regulations for 3D printed medical devices are based on different medical device categories depending on what part of the world or what nation it has been manufactured in, or just imported to. In this section the thesis will mainly focus on the regulations around the EU's EMA, EC and the FDA, with some mentions about other regulatory bodies, as they are of greater interest concerning this thesis.

Standards for 3D printed devices are compliance with industry-specific quality standards. For instance, ISO 13485, Medical devices - Quality management systems - Requirements for regulatory purposes for medical devices, ISO 9001, Quality management systems - Requirements for general manufacturing, or ISO 22000, Food safety management for food safety. Ensuring the materials used in 3D printing meet safety and quality standards is crucial. Material properties, safety, and biocompatibility may be regulated or certified. Intellectual Property (IP) Laws are critical when printing items based on patented designs. Companies and individuals should respect patents, copyrights, and trademarks. Safety and Performance Testing for critical applications like aerospace or medical devices are needed. (U.S. FOOD & DRUG Administration 2023.) Extensive testing is required to validate the safety and performance of 3D printed items. Manufacturers and designers of 3D printed items must adhere to regulation norms of liability in case of harm or defects. Compliance with environmental regulations is essential, especially in industries where hazardous materials or waste are generated in the printing process. (Contardi, M. 2019.)

Examples of 3D printed medical devices include patient-specific implants such as hip or knee implants, as well as cranial implants customized to fit a specific patient's anatomy. Prosthetic limbs, such as hands or legs, can be designed to match the unique shapes of a patient's body. Additionally, dental implants aid in treatment planning, while drug delivery devices like 3D printed tablets and capsules enable personalized drug dosages. Custom-made hearing aids can

also be a 3D printed medical device, offering a more discreet appearance and a more compact design. (Lundy, D. 2022.)

The difference between a medical device and tool are the intended use, as tools are used in non-medical contexts and are not subject to the same regulatory requirements as medical devices. Medical devices are usually intended for medical treatment or diagnosis, to treat, monitor or prevent medical conditions. (EMA n.d.b.)

While writing this thesis, there is a global trend towards strengthening regulations for medical devices to enhance patient safety and improve regulatory oversight. Regulatory bodies or agencies may introduce stricter requirements for clinical evidence, post-market surveillance, and quality management systems. Some regulatory unification goals for medical devices (including 3D printed ones) aim to align medical device regulations across different regions, to facilitate international trade and to streamline the regulatory process to make it easier for regulation agencies and manufacturers. Efforts to harmonize regulations will continue and evolve, particularly between major markets like the United States, European Union, Asia and other regions of the globe. (Contardi, M. 2019.)

3.1 3D printed medical device regulations now

The regulations for 3D printed medical devices are always evolving with time as technological advances and new ways to implement 3D printing are discovered, with medical devices being one of the most anticipated technological branches for 3D printing. (FDA 2017.) So, the regulations will evolve in time, but when writing this thesis there are same sort of regulations with 3D printed medical devices and other medical devices, with some upcoming exceptions with manufacturing and providing safe 3D printed devices. With involving and evaluating manufacturing methods and quality control regulations with 3D printed devices. (Mamo, H.B. etc. 2023.)

Some used regulations from and for different agencies are the International Organization for Standardization (ISO), American Society for Testing and Materials (ASTM) standards, and so on. (ISO n.d.) These are mainly for the manufacturing of 3D printed medical device and worthwhile of considering:

FDA's Technical Considerations for Additive Manufactured Medical Devices:

While not an ISO standard, the U.S. FDA has issued technical considerations specific to additive manufactured medical devices, which include 3D printed medical devices. It outlines the agency's recommendations for manufacturers in this field. It addresses design, manufacturing, testing, and quality system considerations specific to additive manufacturing technologies. (FDA 2017.)

Regulation of 3D Printed Devices in Australia:

The TGA in Australia provides guidance on the regulation of 3D printed medical devices. This guidance outlines the regulatory requirements for manufacturers seeking to market 3D printed devices in Australia. (TGA 2023b.)

Guidance Document - Software as a Medical Device (SaMD):

Health Canada provides guidance on the regulatory requirements for software used as a medical device, which can be relevant to 3D printed medical devices with software components. (Health Canada 2023.)

Guidance on Classification Rules for In Vitro Diagnostic Medical Devices under the IVDR:

The MDCG in the EU issues guidance documents related to medical devices, including those incorporating 3D printing technology. (Hall, A & Payne, S. 2018.)

ISO 13485:2016

ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes: This is the international standard for

quality management systems specific to the design, development, production, and distribution of medical devices. Compliance with ISO 13485 is a common requirement for medical device manufacturers, including those producing 3D printed medical devices. (ISO 13485.)

ISO/ASTM 52900:2021(en)

ISO/ASTM 52900:2021(en) Additive manufacturing - General principles - Terminology: This ISO/ASTM standard provides a standard terminology, classification system, and reference document for additive manufacturing technologies, including 3D printing. It helps to establish common language and definitions for the field of additive manufacturing. (ISO/ASTM 52900.)

ISO 14971:2019

ISO 14971:2019 Medical devices - Application of risk management to medical devices: This standard outlines the process for risk management of medical devices. Manufacturers of 3D printed medical devices need to conduct risk assessments and implement risk management processes to ensure the safety and effectiveness of their products. (ISO 14971.)

ISO 10993-1:2018

ISO 10993-1:2018 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process: This series of standards addresses biological evaluation of medical devices, including 3D printed devices. It provides guidance on testing for potential biocompatibility risks of medical devices on living tissues. (ISO 10993-1.)

ASTM F2792-12

ASTM F2792-12 Standard Terminology for Additive Manufacturing Technologies: This standard provides guidelines for the characterization of properties of 3D printed materials for medical applications. It helps evaluate the mechanical, physical, and thermal properties of materials used in 3D printing for medical devices. (ASTM F2792)

ASTM F3291-17

ASTM F3291-17 Standard Test Method for Measuring the Force-Resistance of a Membrane Force Sensor: This standard outlines the requirements for manufacturing and testing of patient-specific 3D printed devices. It provides guidance on the design, fabrication, and verification of patient-specific 3D printed medical devices. (ASTM F3291.)

ASTM F3091/F3091M-14(2021)

ASTM F3091/F3091M-14(2021) Standard Specification for Powder Bed Fusion of Plastic Materials: This standard provides guidelines for the material extrusion process used in 3D printing medical devices. It addresses considerations related to materials, printing parameters, and post-processing. (ASTM F3091.)

ISO 22442-1:2020

ISO 22442-1:2020 Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management: This standard addresses the risk management process for medical devices that incorporate animal tissues or their derivatives, such as tissue-engineered products used in 3D printed medical devices. (ISO 22442-1.)

ISO 17327-1:2018

ISO 17327-1:2018 Non-active surgical implants Implant coating Part 1: General requirements: This standard provides general terminology and definitions related to additive manufacturing, which is essential for clear communication in the field. (ISO 17327-1.)

ASTM F2971-13(2021)

ASTM F2971-13(2021) Standard Practice for Reporting Data for Test Specimens Prepared By Additive Manufacturing: This standard provides guidelines for the AMF file format, which is used to describe 3D models for 3D

printing. Standardizing the file format enhances interoperability and reduces potential errors in the manufacturing process. (ASTM F2971.)

ASTM F3122-14(2022)

ASTM F3122-14(2022) Standard Guide for Evaluating Mechanical Properties of Metal Materials Made via Additive Manufacturing Processes: This standard specifically focuses on the evaluation of mechanical properties of 3D printed porous titanium scaffolds used in medical applications. (ASTM F3122.)

ASTM F3203-19

ASTM F3203-19 Standard Test Method for Determination of Gel Content of Crosslinked Polyethylene (PEX) Pipes and Tubing: This standard helps in the selection of appropriate lubricants used in 3D printing processes to ensure the quality and safety of the final medical device. (ASTM F3203.)

ASTM F3311-19

ASTM F3311-19 Standard Practice for Mat Bond Evaluation of Performance and Compatibility for Resilient Flooring System Components Prior to Installation: This standard provides a test method for evaluating the effects of extruding additives on the fusion and mechanical properties of 3D printed materials used in medical devices. (ASTM F3311.)

Manufacturers of 3D printed medical devices should be aware of these standards and other relevant guides or guidelines, to ensure compliance with regulatory requirements in the targeted area and meet the highest safety and quality standards for their products. There can be more in-depth regulations depending on where the medical device will be used, with data handling depending on the regulation agencies.

3.2 How different materials and drugs affect regulations

Regulations governing the 3D printing of medical devices often depend on their intended usage and the materials employed. Some materials utilized in 3D

printing include drugs, which can introduce additional effects atop the properties of the materials used in the devices. So, it is important to know what kind of material is used for the 3D printed medical device. If drugs are used in the medical device manufacturing, it is important to know what kind of drug is used. As there are regulations of what kind of drugs and materials can be use inside and out of bodies. (FDA 2017.) There are limitations on what materials can be used inside a human or animal body, as some can be harmful to the body. (Contardi, M. 2019.)

The utilization of drugs operates within a distinct regulatory framework, given their independent regulation and requirement for technical data. When drugs are integrated into a 3D printed medical device, both tested and untested drugs can notably increase the device's risk classification, solely due to the inclusion of the drug component. (Contardi, M. 2019.)

The choice of materials and drugs used in 3D printed medical devices can significantly affect their regulatory status and compliance with regulations in the EU and FDA. The regulatory considerations for 3D printed medical devices are complex and depend on multiple factors, such as the intended usage, risk classification, and the characteristics of the materials or drugs utilized. There are some key points to consider as materials and drugs that are known, or unknown are used in tandem with 3D printing medical devices. (Contardi, M. 2019.)

As the first keynote both the EU and FDA have strict requirements for the biocompatibility of medical device materials, as the 3D printed medical devices must be made from materials that are safe and compatible with the human body. 3D printed medical device manufacturers need to conduct biocompatibility testing to assess the potential for adverse biological effects of the materials and demonstrate their safety for the intended use. (Contardi, M. 2019.)

Second keynote is the material characterization as the EU and FDA expect comprehensive characterization of 3D printing materials, including their mechanical properties, chemical composition, how they degrade, and their

stability of use. The manufacturers of the 3D printed medical devices need to provide detailed information about the properties of materials used in manufacturing medical devices, to be compliant to the regulatory manufacturing and documentation of medical devices. (Contardi, M. 2019.)

Next keynote is the drug to device combination, where 3D printed medical device incorporating drugs or biologics (such as pharmaceuticals, growth factors, or living cells) may be considered a drug-device combination product. In such cases, additional regulatory requirements apply, as both the medical device and the drug component need to meet their respective regulations to be accepted or processed. (Cohen, I.G. ect. 2022.)

If the 3D printed medical device uses any sort of drugs, there should also be an implemented and tested drug release and dosage control. For drug-device combination products, precise control of drug release and dosage is crucial, and the regulatory authorities will require data on drug release kinetics and dosage accuracy to ensure safe and effective drug delivery to ensure the safety of the device. (Contardi, M. 2019.)

As different materials or drugs can be combined in the production of a 3D printed medical device, there should naturally be a Good Manufacturing Practices (GMP) compliancy. As GMP is essential to produce medical devices and pharmaceuticals, and the manufacturers must comply with GMP regulations to ensure consistent and high-quality production of 3D printed medical devices that incorporate drugs or biologics. (EMA n.d.a.)

As mentioned before, both the EU and FDA emphasize post-market surveillance for medical devices, as it is a growing trend to have consistent data from a longer interval than before. Manufacturers of 3D printed medical devices must establish post-market monitoring systems in order to track the performance and safety of their devices, especially when drugs are involved. (FDA 2018; EMA n.d.b.)

Manufacturers should be aware that changes in materials or drug formulations after market approval may trigger regulatory actions, as the post-market

changes may require additional assessments, submissions or updates to the device's documentation for calculating the risk and to be approved for use. (Contardi, M. 2019.)

The EU and FDA have also implemented the UDI system for medical devices to enhance traceability and post-market surveillance of the medical device, and the manufacturers must assign a unique identifier to their 3D printed medical devices to comply with UDI regulations even if it can bring more work with it. (GS1. n.d.)

Regulatory authorities will also require clinical evidence to support the safety and efficacy of 3D printed medical devices, especially those involving new or not tested materials or drug delivery. Clinical trials may be necessary for some 3D printed medical devices, depending on the level of risk and novelty of what the medical device has been implemented with. (FDA 2017; EMA n.d.b.)

It's important for medical device manufacturers to engage early with regulatory authorities, such as EMA in the EU and the FDA in the United States, to ensure proper understanding and compliance with the specific regulations relevant to their 3D printed medical devices that involve different materials or drugs. Detailed documentation and scientific data will be essential to demonstrate the safety and performance of these devices, for approval of use or testing. (Cohen, I.G. ect. 2022.)

If the 3D printed medical device requires sterilization, manufacturers must provide evidence that the chosen materials for the medical device can withstand the chosen sterilization method without compromising their properties or safety. Sterility assurance is crucial for implantable or invasive devices that come to contact with the patient. (EMA n.d.)

For 3D printed medical devices that come into contact with the body or body fluids, manufacturers need to assess the potential for material toxicity and the release of leachable or extractables from the materials into the body This

information is critical for biocompatibility assessments and to ensure the risk classification of the device. (FDA 2017; EMA 2020.)

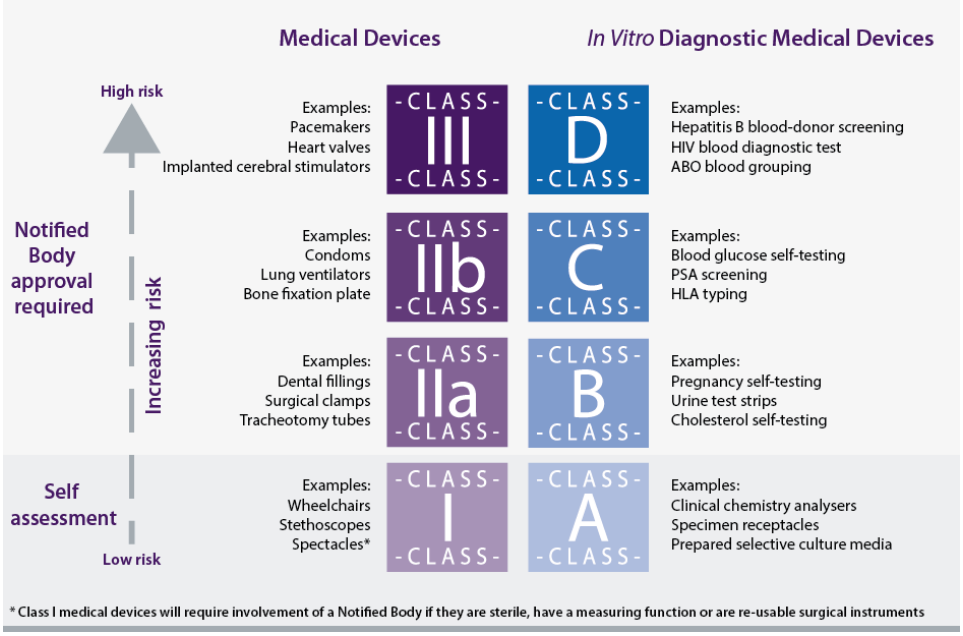

Figure 4. Comparison for Medical Devices and In Vitro Medical Devices (Hall, A & Payne, S. 2018).

If the 3D printed medical device is used In Vitro diagnostics it can affect the classification, as seen in the Figure 4. For example, when the medical device is in contact with blood its risk classification goes up with the IVDR. If nanomaterials are used in 3D printed medical devices, additional considerations come into play due to their unique properties and nanomaterials new ways of use in research. Nanotechnology-based devices may require specific and more strict safety assessments to address potential risks associated with nanoparticles. (Hall, A & Payne, S. 2018.)

For 3D printed medical devices involving drugs or biologics as materials or functioning part of the device, manufacturers need to demonstrate the stability and shelf life of the product. Information on degradation rates and potential changes in drug activity over time is essential for regulatory submissions and approval to use. (Contardi, M. 2019.)

The classification of drug-device combination products can be complex, and regulatory authorities may require manufacturers to provide a clear justification for the chosen classification, as the device classification determines the regulatory pathway for market approval and what the manufacturers must do. The documentation required for regulatory submissions for the regulatory bodies in the EU and FDA can be extensive, especially for 3D printed medical devices that involve novel or new materials or an implemented drug delivery system. Medical device manufacturers must provide comprehensive data and evidence to support safety and effectiveness for the claims for the medical devices. (Contardi, M. 2019.)

When a 3D printed medical device incorporates a drug or medicinal substance for In Vitro diagnostic purposes, it may be classified as a combination product. Combination products are subjected to specific regulatory requirements that consider both the device and drug components, with their own limitations. Combination products require a unique regulatory pathway that involves coordination between the regulatory authorities responsible for both drugs and medical devices, which manufacturers must navigate with specific requirements of both categories to obtain marketing approval. (EMA 2020.)

The presence of drugs or substances in 3D printed medical devices may necessitate additional testing and validation to ensure compatibility, stability, and effectiveness. Manufacturers must provide evidence of the device's performance and its interaction with the incorporated drugs or substances. Continuous monitoring of combination products is critical for identifying and addressing any potential safety concerns or adverse events that may arise after the device's approval and market release. (EMA n.d.)

3D printing introduces unique manufacturing challenges, such as process validation, repeatability, and reproducibility. Regulatory authorities may request additional information related to the 3D printing process and its impact on device performance. (Cohen, I.G. ect. 2022.)

Personalized 3D printed medical devices are uniquely designed for individual patients based on their medical imaging data or other patient-specific information usable for designing the 3D medical device. This introduces variability and customization, which can make it challenging to apply traditional regulatory pathways designed for standardized devices but having an almost unlimited possibilities for treatment. (Cohen, I.G. ect. 2022.)

Personalized medical devices may not fit neatly into existing regulatory pathways as both the EU and FDA have recognized the need for more flexible and adaptive regulatory approaches to accommodate personalized medical devices. With risk classification the patient-specific nature of these devices can of course influence their risk classification and in some cases, personalized devices may be considered to have higher risk due to the potential for variability and the need for precise fit and function for a specific job. (EMA n.d.)

Personalized medical devices also often require clinical evidence specific to each patient or a patient subgroup, and this may necessitate additional clinical studies or real-world data collection to demonstrate safety and effectiveness of the personalized and 3D printed medical device. (Cohen, I.G. ect. 2022.)

While both the EU and FDA have their regulatory requirements, there are ongoing efforts for international harmonization of medical device regulations around the globe. Medical device manufacturers should consider global trends and initiatives that may influence future regulatory requirements, depending on where their medical device could end up. (Contardi, M. 2019.)

It is important for manufacturers to engage early with regulatory authorities, such as the EMA in the EU and the U.S. FDA, or other regulatory body to ensure proper understanding and compliance with the specific regulations relevant to their 3D printed medical devices that involve different materials or drugs. Detailed documentation and scientific data will be essential to demonstrate the safety and performance of these devices to the designed market. (CMS 2020.)

Seeking expert advice during the development of 3D printed medical devices that involve different materials or drug delivery is crucial. Understanding the specific regulatory requirements and conducting thorough assessments of the materials' impact on safety and performance are vital steps to ensure successful market approval and compliance. (Formlabs. n.d.)

As a side note there are updates to regulations in other parts of the world besides the ones focused on this thesis. As Brazilian ANVISA is updating their regulation of medical devices to be more specific for registration, with the previous regulations being labeled insufficient for current devices. The ANVISA deadline has been implemented in the year 2023. (ANVISA. n.d.)

Chinas NMPA is also releasing an update for medical device standards on November 18th of 2022, with the idea of changing product types and standards. Aiming to make them potentially safer and easier to use, with also an updated electromedical safety standard. (BG 9706.1-2020.)

3.3 Anticipated 3D printed medical device regulations

Over the past five years, there have been significant changes in the regulation of medical devices (including 3D printed ones) in various regions around the globe. While the specific changes may vary by country or regulatory authority, there are some trends and developments observed during this period. (Cohen, I.G. ect. 2022.)

One trend was the European Union updating the previous Medical Device Directive (MDD) to the Medical Device Regulation (MDR) as introduced in 2017, replacing the MDD. The MDR brought several changes, including increased scrutiny of clinical evidence, strengthening post-market surveillance requirements, and stricter regulations for high-risk devices, as it aimed to enhance patient safety and to improve the transparency and accountability of medical device manufacturers. (Bianchini, E & Mayer, C.C. 2022.)

In the United States the FDA implemented MDSAP in 2017, where the MDSAP allowed recognized auditing organizations to conduct a single audit. Aiming to assess compliance with quality management system requirements in many countries, streamlining the audit process for manufacturers operating in participating jurisdictions. (Inter-American Coalition n.d.)

The adoption of UDI had also gained momentum worldwide, as UDI aims to provide a unique identifier for each medical device to improve traceability, post-market surveillance, and adverse event reporting. Many countries and regions, including the United States, European Union, and Australia, have implemented or are in the process of implementing UDI requirements for a more global efficiency. And as seen on the Figure 5, the EU is implementing this wihile also having the European EUDAMED in use. (Contardi, M. 2019.)

The rise of digital health technologies and software-driven medical devices had pushed many regulatory agencies to develop new or specific frameworks to address the unique challenges of these medical devices. Even the FDA released several guidance documents related to software such as the SaMD, or Clinical Decision Support (CDS) tools, and digital health innovation. Aiming to provide clarity on regulatory requirements for these sorts of devices. (Cohen, I.G. ect. 2022.)

While writing this thesis, the medical device scenery is changing every year as technology is advancing and the personification of medical devices has been a growing trend, since it can help the patients to have treatments faster and more personalized. While writing this thesis there is a global trend towards strengthening regulations for medical devices to enhance patient safety and improve regulatory oversight. (Wizemann, T. 2010.) Regulatory bodies or agencies may introduce stricter requirements for clinical evidence, post-market surveillance, and quality management systems. The European Commission new regulations and features coming with the MDR and IVDR updates are shown in the Figure 5. These key features are design to make medical device regulations more robust as well as increasing patient safety. (Byrne, R. 2019.)

Figure 5. Key features of new regulations related to medical devices and In Vitro diagnostics (Byrne, R. 2019).

There are some regulatory unification goals for 3D printed medical devices as there are for other medical devices, to align medical device regulations across different regions, facilitate international trade and streamline the regulatory process to make it easier to all nations. As seen on the Figure 5, the EU regulations are aiming for improved transparency and traceability, with no ambiguity. Efforts to harmonize regulations will continue and evolve, particularly

between major markets like the United States, European Union, Asia and other regions of the globe. (Byrne, R. 2019.)

As 3D printed medical devices become more connected and reliant on digital technologies and the internet or just coding, cybersecurity threats become a significant concern. On this topic regulatory bodies may highlight cybersecurity requirements to ensure the security and privacy of patient data, device safety and mitigate the risk of cyber-attacks. (Cohen, I.G. etc. 2022.)

There is also increased scrutiny of complex software and AI-based devices with the rise of software-driven medical devices and use of artificial intelligence (AI) in applications for healthcare. Regulatory bodies may develop specific frameworks to address the unique challenges associated with these technologies and this may include regulations for validation, transparency, and post-market monitoring of software and AI algorithms used in medical devices directly or indirectly. (Cohen, I.G. etc. 2022.)

The merging of different technologies, such as 3D printing, nanotechnology, drugs, and regenerative medicine, is likely to influence medical device regulations. Regulatory bodies or agencies will have to assess the safety, efficiency, and quality control measures specifically to implement these technologies. As the demand for new and improved medical devices grows, regulatory bodies overseeing medical devices might establish expedited pathways for innovative and breakthrough technologies. This approach enables faster market access for devices addressing critical, unmet medical needs. (Bianchini, E & Mayer, C.C. 2022; Cohen, I.G. etc. 2022.)

There has also been an increased emphasis and demand on post-market surveillance for medical devices and vigilance to monitor the safety and performance of medical devices once they are on the market and not just when they are assured. Regulatory agencies around the globe are working towards strengthening post-market surveillance systems, promoting better reporting of unpleasant or adverse events, and enhancing the exchange of safety information between regulatory authorities. As authorities are aiming to make

medical devices safer for patients in the long run. (Bianchini, E & Mayer, C.C. 2022.)

As mentioned before, there is an ongoing focus and drive on harmonizing medical device regulations across different regions around the globe to facilitate global market access. And the harmonization efforts aim to reduce manufacturer’s or researchers' regulatory burdens, streamline the processes, and align needed medical device requirements across different nations or area jurisdictions. (Vivek, D etc. 2019.)

Off course these trends and planned unifications are not without challenges or possible consequences, as the Covid-19 outbreak postponed quite a lot of documentation and deadlines of EU regulatory changes in the implementation of the MDR and IVDR. The timeline of the MDR and IVDR in EU has been delayed by Covid-19, for there was a focus on responding to the pandemic, and to get diagnostic tests and personal protective equipment approved fast. (Directorate-General for Health and Food Safety 2023.)

Emergency usage and temporary approvals were used as well to address urgent public health needs, with some medical devices being used without full compliance with standard regulatory requirements. There were some positive outcomes for this as collaboration with regulatory bodies were increased and it served as testing regulatory flexibility in a crisis, to give a more robust system. (Bianchini, E & Mayer, C.C. 2022; Cohen, I.G. ect. 2022.)

Because of Covid-19 the FDA also had to use emergency authorizations and expedited pathways to address public health emergencies, with increased collaboration with different agencies. There was also an increase of virtual or remote regulations for the FDA and EU due to travel and safety restrictions. (Cohen, I.G. ect. 2022.)

At the time of writing this thesis, there are also challenges posed by an ongoing war in Europe. These challenges have global implications and may contribute to increased discrimination against nations, potentially affecting the harmonization of medical device regulations in the near future. (McGowran, E. 2023.)

There could also be possible indirect effects of climate change. As increasingly severe climates and other impacts influence the demand for medical devices or drugs in various regions around the world, particularly during emergencies or supply chain disruptions. (Titerlea, V. 2022.)

As an important note that these potential changes and anticipations are speculative and should not be considered definitive predictions since actual changes in medical device regulations will depend on the decisions and priorities of regulatory authorities worldwide in response to evolving healthcare needs and technological advancements. To stay updated with the specific regulatory agencies in which the wanted information is needed, the regulatory agencies web sites should be with information regarding updates. (Vivek, D etc. 2019.)

4 Conclusion

3D printed medical devices have been available for some time and they are evolving quite rapidly to meet needs and expectations of patients, researchers, manufacturers, and other people involved in 3D printing or medical device field. As mentioned before, the medical device regulations are updating and evolving as there is a need for more transparent regulations and clear defining of what makes something like 3D printed device a medical device, and how it can be changed with used materials or intended usage.

3D printed medical devices have almost limitless potential for personalization to suit a patient's needs or specific uses, depending on the materials and designs that can be employed in their manufacture. Therefore, regulations are updating to tackle the evolving 3D printing of medical devices with more precise basic regulations that can be used more flexibly depending on the situation and a clear segmentation of low risk to high-risk devices in the EU and FDA. In the master’s thesis of Heini Sahlberg the writer also mentions that the newer regulations in the EU will ensure safer and efficient devices in the market. He also mentions of stricter requirements in the MDR and IVDR. Even tough Heini Sahlbergs thesis focuses on the software development for the company she made it for, there seemed to be similar ideas in the vast array of standards and harmonization in regulations. (Sahlberg, H. 2020.)

The FDA in the US has also been updating their risk classifications and FDC Act and the CFR, for the same reasons to tackle evolving technology in the medical field. So any major changes coming in the EU and US besides those mentioned before, will take some time, and will be informed well in advance. Because manufacturers and regulatory bodies in the EU and US are filled with work, with updating the older medical device approvals to the new system of regulation. There is no rush to update the now implemented regulations in the EU and US. There will be smaller updates and fine tuning in the laws and regulation of 3D printed medical devices in the EU and US and even other countries. The regulatory bodies and agencies are informing what is tweaked in

their documents on their websites as the transition time to the newer regulations are going forward.

In the article of Finnish Journal of eHealth and eWelfare, Medical device manufacturers preparation for the new Medical Device Regulation (MDR), the writer says that the information of MDR is fragmented and not so easy to find. however it didn't seem to be too hard to find when writing this thesis. As they focused on the information that Finnish medical device manufacturers have about the MDR, they did seem to see the potential of a harmonized regulation front for manufacturers. The article suggested that studies involving medical devices could have an integrated course for regulation and how to update regulation information. (Huusko, J.; Kinnunen, U-M & Saranto, K. 2020.) That sounds like a good idea, as it could help in the regulation knowhow when working in the medical devices field.

Both the EU and FDA have taken steps to address the regulation of personalized medical devices, recognizing their potential benefits and challenges (mainly in 3D printed ones). Regulatory agencies are working to provide guidance and adapt their approaches to accommodate the unique and chancing aspects of personalized medical devices while ensuring patient safety and product effectiveness. The guidance and consultation to manufacturers and researchers of 3D printed medical devices is helpful, so they know what steps and documentation they need to ensure their work can go forward. As new medical devices should be inputted to registry in good time. For the manufacturers and researchers, the best way to get confirmation, information or help in the subject is to be directly in contact with the intended regulation agency. This is recommended at least if the subject for documentation is hard to categorize with the upcoming regulations.

3D printed medical devices with drugs or similar substances are more strictly monitored and tested with usually their own pathway for regulation approval, as the devices In Vitro can be more harmful (with higher risk to patients) if either part of this combination medical device fails. So, manufacturers or researchers should follow the FDA's regulations and EU's MDR and IVDR with the

combination device regulations. With some possible regulation agencies notified bodies involvement in assessing some more hazardous substances.

As a note, one can also engage a regulatory consulting firm to be kept informed about evolving regulations and standards. These firms offer a range of services to assist medical device manufacturers in navigating the intricate and continually evolving regulatory environment, ensuring compliance with the requirements of various regulatory authorities worldwide. (Kasve 2023.)

With the data available now, one can anticipate upcoming updates for 3D printed medical device regulations, as well as other medical devices. The trend seems to be globally of harmonizing regulations, standards, and risk classifications. With data gathering, documentation, conducting clinical trials, providing evidence of performance, and implementing stricter requirements for patient safety and traceability as top priorities.

Personalized medical devices regulations will also be stricter, unless it they are low-risk devices with no combination aspects, as they will be more promptly available for use with the rise of 3D printing. Regulatory authorities may still require evidence of design and validation for each personalized device in the near future, until different substances and methods of 3D printing have enough clinical trials and data to confirm that they are safe to use. If a vast number of substances and methods of 3D printing are validated, that could potentially make customization for 3D printed medical devices more readily available with those substances.

It could be anticipated that low-risk 3D printed medical devices will be easier to be approved and high-risk medical devices will be more strictly investigated before approval with upcoming regulations. 3D printed medical devices should be assessed and registered a good amount ahead of time, as approval of regulation agencies can take time with all the updating and obligatory registering.

In table 2 a PESTEL analysis on 3D printed medical devices is presented in order to help grasp the future factors of 3D medical device manufacturing. The PESTEL is a summary of the literature search made for this thesis.

Factors	Impacting factors and trends	What to do for the future
Political	Government agencies, such as the FDA in the United States and the EMA in the EU, play a significant role in approving and regulating medical devices. Changes in regulatory requirements can impact the development and commercialization of 3D printed medical devices. Trade agreements and tariffs can affect the import and export of 3D printed medical devices, influencing market access and competition.	Stay up to date in regulatory changes and plan your development accordingly. Stay updated on market accesses and competitions.
Economic	The healthcare industry's growth and economic stability influence the demand for medical devices, including 3D printed ones. Economic considerations, such as cost savings and the affordability of 3D printing technologies, can impact adoption rates.	Research and optimize production, if possible, a product that is economically stable and cheap could be in demand at any time.
Social	The aging population in many countries drives the demand for medical devices. 3D printed devices may offer innovative solutions to address the healthcare needs of an older demographic. Growing patient preferences for personalized medical solutions can drive the adoption of 3D printed devices tailored to individual needs.	Easy to use or personal equipment are on the rise, as they can be more comfortable to use. Innovations are key if they can make the products easier to use or make.
Technological	Ongoing advancements in 3D printing technologies, including materials and printing techniques, can lead to improved device design and manufacturing processes. The integration of 3D printing with digital health technologies, like telemedicine and wearable devices, can transform patient care and medical device design.	Being up to date and advancing in additive manufacturing is a key factor as research and development is time consuming. Digital health technologies should be made safe before making them into a standard. Including cyber security and AI usage validation.
Environmental	3D printing can potentially reduce material waste compared to traditional manufacturing methods, making it more environmentally sustainable. The environmental impact of 3D printing materials and the recycling of medical devices should be considered to meet sustainability goals.	Research on fully recyclable materials that are based on renewable resources, or biodegradable material. With 3D printers and materials made with low environmental impact resources. Reusing old devices or materials in different ways could help reduce the environmental footprint.
Legal	Intellectual property rights, including patents and copyrights, play a role in protecting innovations in 3D printing and medical device design. Legal considerations around product liability and adherence to quality standards are crucial in ensuring patient safety and compliance with regulations.	Having legal understanding or a place where you could easily get help on property rights can help. Patents should be made and legality in different continents checked. Regulations are important to be acknowledged depending on the marketed area.

Table 2. Pestel analysis of 3D printed medical devices.

It's important to note that medical device regulations and requirements may evolve over time. The websites of different countries regulatory bodies can be checked for relevant regulations, guidance documents, and notifications for the most up-to-date and accurate information on the regulations for 3D printed medical devices.

In the Frontiers in Bioengineering and Biotechnology, Volume 11 article: Legal issues and underexplored data protection in medical 3D printing: a scoping review, they seemed to focus on the legal issues involving 3D printed medical devices. Main point of the article was that there is unclear legislation of custom-made and patient-matched devices, which could be an issue as they concluded a need for uniformity in terminology with medical 3D printing. (Pettersson, A.B. etc. 2023.) Uniformity sounds like a good idea to implement for 3D printed medical devices, as it would make it easier to harmonize research and development.

The article Bianchini, E., Mayer, C.C. Medical Device Regulation: Should We Care About It? Has good points on how the scientific community need to have clear regulations to reduce risk of new and old devices, as patient safety is important. (Bianchini, E & Mayer, C.C. 2022.) I concur as in this thesis the patient safety is one of the most important things about regulations and shouldn’t be seen as an obstacle as said in the article.

The study of additive manufacturing for medical devices and regulations could be honed to different continents and be studied more of the possible harmonization, as a continuation for this study. Examples for this are Asia and South America with interesting associations to harmonize their regulations, and the continent of Africa have some of their own regulation bodies that the thesis didn’t have room for.

5 Summary

3D printing or additive printing is an evolving technology with potential in the field of medical devices, that need new regulations to ensure the safety of patients in research and manufacturing.

The medical device regulation bodies in different countries and regions seem to be harmonizing on some level of risk classifications and regulations. It also seems to be a trend to make manufacturing and development of medical devices (including 3D printed ones) more accessible. The implementation of UDI aims to provide a unique identifier for each medical device to improve traceability, post-market surveillance, and adverse event reporting.

The thesis primarily centers on the evolving regulations governing 3D printed medical devices within the EU and the US. These regulations are undergoing updates to address advancements in technology and prioritize patient safety, encompassing areas such as AI, 3D printing, digital software, cybersecurity, and more. The use of diverse materials and drugs with 3D printed medical devices can drastically affect their risk classification. New materials or drug integration may heighten risks due to limited usage history, while drug inclusion brings additional regulatory considerations. However, personalized 3D printed devices might lower risk classifications in specific cases. EU and US are big motivators for other regions to cooperate as they are one of the biggest medical device markets.

The regulatory agencies are working to provide guidance and adapt their approaches to accommodate medical device manufacturers and researchers. The best way to get information or help in the subject is to be directly in contact with the intended regulation agency. This is a living and evolving subject that should be updated on, if manufacturing or researching 3D printed medical devices. As the regulations can be subjects to tweaks and updates, for time to time. If one is not capable of following regulations for some reason, there are regulation consultation companies to turn to.

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The following tools have been used in writing the thesis:

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