D7.1 Report on key regulatory requirements for materials and processes

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List of Acronyms

Acronym	Description
AMF	Additive Manufacturing File
ASTM	American Society for Testing and Materials
ATMP	Advanced Therapy Medicinal Products
CDRH	Centre for Devices and Radiological Health
CEN	European Committee for Standardisation
CENELEC	European Committee for Electrotechnical Standardisation
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CMD	Custom-made devices
CoA	Certificates of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CT	Computed tomography
DLP	Digital Light Processing
DQ	Design Qualification
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FDM	Fused Deposition Modelling
FTIR	Fourier Transform Infrared Spectroscopy
GMP	Good Manufacturing Practices
GPC	Gel Permeation Chromatography
HCT/P	Human Cells, Tissues, and Cellular and Tissue-Based Products
ICH	International Council for Harmonisation
iPSC	Induced pluripotent stem cells
IQ	Installation Qualification
ISO	International Organisation for Standardisation
JRC	Joint Research Centre of the European Commission
LAL	Limulus Amebocyte Lysate
MCB	Master Cell Bank
MDD	Medical Devices Directive
MDPS	Medical Device Production System
MDR	Medical Device Regulation
NB	Notified Body
NMR	Nuclear Magnetic Resonance
OQ	Operational Qualification
PCL	Polycaprolactone
PDE	Permitted daily exposure
PHS	Public Health Service
PLGA	Poly(lactic-co-glycolic acid)
PMA	Premarket Approval
PMOA	Principal mode of action
POC	Point-of-care
PQ	Performance Qualification
PSIS	Putting Science Into Standards

QMS	Quality Management System
SAL	Sterility Assurance Levels
SLA	Stereolithography
SLS	Selective Laser Sintering
SVF	Stromal Vascular Fraction
TGA	Therapeutic Goods Administration
UDI	Unique Device Identification
WCB	Working Cell Bank

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Definition list

- *Urethral Strictures:*
  A stricture is a narrowing in a tube-like passage in tubular organs such the urethra [1].
- *Additive manufacturing:*
  Additive manufacturing is the general term for those technologies that, based on a geometrical representation, create physical objects by successive addition of material [2].
- *3D printing:*
  Fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology [2].
- *Biomaterial:*
  A biomaterial is a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. (Definition proposed by the *European Society for Biomaterials Consensus Conference II* [3])
- *Bioink:*
  Printable material formulation used in a 3D bioprinting process, consisting of biomaterials, biologics, and/or living components such as cells. (Definition proposed by the authors of this deliverable)
- *3D bioprinting:*
  The process of 3D printing in which a bioink, consisting of biomaterials, biologics, and/or living components such as cells, is used to fabricate structures for applications in biomedicine and the life sciences. (Definition proposed by the authors of this deliverable)

Disclaimer

1. Executive Summary

The STRONG-UR project aims to develop a single stage, regenerative medicine solution for the treatment of unilateral male urethral defects and associated fistulas. The approach integrates autologous cells with a hydrogel platform to formulate a patient-specific bioink, which is deposited intraoperatively using a handheld bioprinting device. This enables real time fabrication of 3D bioprinted tissue constructs tailored to the patient's anatomical defect, representing a disruptive shift from conventional implant manufacturing toward personalised, on-demand tissue engineering.

The rapid evolution of additive manufacturing technologies, bioinks, and hybrid biological–material systems introduces significant regulatory complexity. While the EU Medical Device Regulation (MDR) 2017/745 has clarified that 3D printed implants are not inherently considered custom-made devices (CMDs), it provides limited guidance on bioprinting workflows involving living cells, novel biomaterials, and decentralised production. Key challenges include determining appropriate device classification, validating dynamic and operator-dependent manufacturing processes, defining quality system requirements across distributed points of care, and assigning manufacturer responsibility when production occurs within a clinical facility.

Several regulatory pathways were examined for their feasibility within the STRONG-UR fast-track model, including the MDR CMD exemption and the ATMP hospital exemption (Article 28, Regulation 1394/2007). However, due to the high-risk nature of bioprinted constructs and the integrated use of cells, biomaterials, and specialised hardware, these routes present substantial limitations. Point-of-care (POC) manufacturing currently appears the most viable option, although it may designate the healthcare institution as the legal manufacturer, thereby transferring full compliance obligations, including risk management, process validation, and quality system implementation.

Overall, the analysis highlights a pressing need for adaptive, process-oriented regulatory and standardisation frameworks capable of accommodating the unique characteristics of 3D bioprinting and personalised biofabrication. This deliverable report (also intended for use as a white paper) outlines the current regulatory landscape, identifies critical gaps at the intersection of bioprinting, quality management, and patient-specific manufacturing, and proposes practical strategic considerations to support regulatory planning for the STRONG-UR single stage therapeutic system.

2. Introduction

Within the STRONG-UR project, the partners jointly strive to develop a revolutionary and innovative treatment for male urethral strictures (Figure 1) using regenerative medicine and tissue engineering strategies. Through the meticulous design of both 3D bioprinting and bioink components, the project aims to make personalised, engineered tissue constructs clinically available. This work is intended to support efforts within the STRONG-UR community to determine which regulatory set-up might be most applicable to the product in development for treatment of unilateral urethral defects. This encompasses STRONG-UR's single stage, or fast-track, approach for repairing fistulas, which may occur secondary to tissue damage associated with urethral strictures (Figure 2), as well because of radiation therapy.

Figure 1: Graphic of male urethral stricture (developed by STRONG-UR Project [1]).

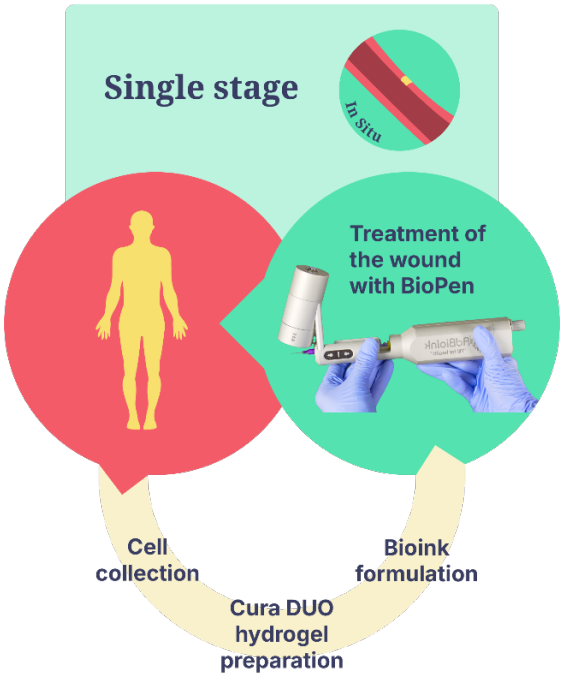

Figure 2: STRONG-UR's single stage fast-track approach for the treatment of urethral fistulas [1] .

In this approach, a bioink is prepared by combining autologous cells with a hydrogel platform (CuraDUO®). During surgery, the tissue defect is repaired using a handheld bioprinter device (BioPen®), which precisely deposits the bioink to create a personalised 3D bioprinted tissue implant made from the patient's own cells.

The rapid development of 3D bioprinting and advanced bioinks is emerging as a disruptive innovation capable of transforming the healthcare industry by enabling personalized, cost-effective devices for point-of-care (POC) use. This paradigm shift moves away from mass-produced, generic devices towards patient-specific, high-performance bioprinted constructs that can be customised during surgery to meet individual patient needs. If properly regulated and standardised, these technologies could significantly improve patient care by making personalised treatments more accessible and affordable. However, current regulatory frameworks are struggling to keep pace.

In the European Union, 3D printed medical devices were historically treated as custom-made devices (CMDs) under the Medical Devices Directive (MDD), exempting them from CE marking and Unique Device Identification (UDI) requirements. The Medical Device Regulation (EU) 2017/745 (MDR) clarifies that 3D printed implants are not automatically considered CMDs and must comply with risk-based classification and regulatory requirements. According to the MDR's Q&A guidance, a 3D printed device only qualifies as a CMD if it is produced based on a written prescription that specifies patient-specific design characteristics, is intended solely for one patient, and is not mass-produced. Many patient-matched devices produced by 3D printing, such as surgical guides or orthopaedic implants manufactured in a range of pre-designed sizes to accommodate different patients, therefore fall outside the custom-made exemption and must follow the standard MDR pathways.

Classification and compliance are determined by risk rather than the printing method or material. Implantable devices are generally classified as Class IIb or Class III depending on how long they remain in the body and whether they are resorbable or release substances. Even without a CE mark, manufacturers must implement a quality management system (QMS) (e.g., ISO 13485) and comply with relevant sterilization (e.g. ISO 14937) and packaging standards (e.g. ISO 11607-1&2). Remaining challenges include validating manufacturing processes and clinical performance, developing standardization, and ensuring robust risk management and quality control. This regulatory uncertainty necessitates the development of specific guidance and standards for 3D bioprinting and bioinks to ensure these innovations are safe and effective [4], [5].

The European Committee for Standardisation (CEN), the European Committee for Electrotechnical Standardisation (CENELEC), and the Joint Research Centre (JRC) of the European Commission have jointly recognised the need for robust standardisation in this emerging field. Their Putting Science Into Standards (PSIS) workshop on 3D bioprinting brought together international experts to identify gaps, priorities, and opportunities for future standards [6]. Likewise, the U.S. Food and Drug Administration (FDA) published a discussion paper on 3D printing medical devices at the POC, further emphasising the importance of establishing a clear and unambiguous regulatory framework capable of supporting disruptive and highly innovative bioprinting technologies [7].

The present deliverable (D7.1) serves as a foundational document, establishing the relevant regulatory landscape and identifying where regulatory and GMP-relevant requirements are expected to arise over the course of product development. In this context, firstly a general overview of the current regulatory landscape and relevant product classifications is presented. The document then outlines the requirements and challenges associated with implementing a QMS system that spans the entire bioink development and 3D bioprinting process. A summary of currently available guidance documents, particularly those referenced throughout the report, is also provided. Finally, the limitations and challenges encountered when applying existing regulatory frameworks to 3D bioprinted products are discussed, followed by several

practical pathways that may be considered when shaping the regulatory strategy for the STRONG-UR single stage approach.

3. Overview of current regulatory landscape

In the field of 3D bioprinting, the wide variety of available technologies, coupled with desired features such as tunability and personalised medical solutions, creates significant challenges for establishing universal standards and navigating the current regulatory landscape. These challenges contribute to the existing technological gap between academic research and clinical or commercial applications. Hence, technical experts are joining forces with regulators and standardisation institutions to draw inspiration from products that have successfully reached clinical use and share technical similarities with bioprinted constructs, such as 3D printed medical devices, injectable hydrogels, and tissue-engineered products [6], [8].

In this section a general overview of the current regulatory landscape for biomedicine products is given. In Europe, the European Medicines Agency (EMA) and in the US, the FDA have established specific standards and guidelines to support harmonisation in the testing of medical devices and materials. These guidelines encompass standards from the International Organisation for Standardization (ISO), the American Society for Testing and Materials (ASTM) and Good Manufacturing Practices (GMP), which together ensure robust quality control systems as well as comparability and reproducibility of results.

3.1. Regulation Categories

The regulatory framework governing bioinks, 3D bioprinted constructs and, the software and hardware involved in 3D printing processes is inherently complex. Therefore, these devices can fall within different regulatory requirements being medical devices, biologics, or combination product depending on whether the final 3D printed product contains cells, tissues, active drug components or other type of additives.

Depending on the material composition and intended purpose, 3D printed constructs can fall into three possible regulatory categories:

3.1.1. Medical Device

The low governing (3D printed) medical devices in Europe are determined by Medical Device Regulation (EU) 2017/745 (MDR) has been in force since 26 May 2017 and fully applicable since 26 May 2021, with transitional provisions running until 2027-2028. Product classification and conformity assess under the MDR 2017/54 are determined through a rule-based system defined in Annex VIII. The intended purpose of device, risk level to the patients, duration and invasiveness of the contact and, type of device (depending on non-active or active components, implantable etc.) are core principles guiding product classification.

When products made through additive manufacturing do not contain any ‘active’ components including biologics or drug components, and their primary mode of action (PMOA) is structural, i.e. mechanical or physical support, they are generally classified as medical devices. A wide

variety of materials fall within this scope, from metal to ceramics to polymers. In the EU, most implantable orthopaedic and orthopaedic-trauma devices are classified as Class IIb or Class III, with similar clinical data requirements [9]. Products manufactured using more complex materials, such as hydrogel scaffolds, polymer-based printed components, and bioinks commonly used in 3D printing, will typically fall into the highest-risk category, Class III.

A general overview of the main stages that are required to reach approval of a medical device is shown in Figure 3. Once a product concludes its feasibility and design stages, it must undergo extensive pre-clinical safety testing as described in ISO 10993. The scope and required tests depend on the intended use, the risk assessment and class of the product, as described in ISO1993-1. The pre-clinical safety evaluation most often includes full chemical characterisation (ISO10993-18) and biological characterisation including biocompatibility testing both *in vitro* (ISO 10993-5) and *in vivo* (ISO 10993-6). Subsequently, a comprehensive clinical evaluation must be performed, with the extent, again, depending on the risk classification of the device. Devices intended for long-term use (> 30 days of tissue/blood contact) are considered high-risk (Class IIb or III) [8], [10].

To obtain market approval, compliance with EU legislation is demonstrated through CE marking, which is granted following mandatory assessment by a Notified Body (NB).

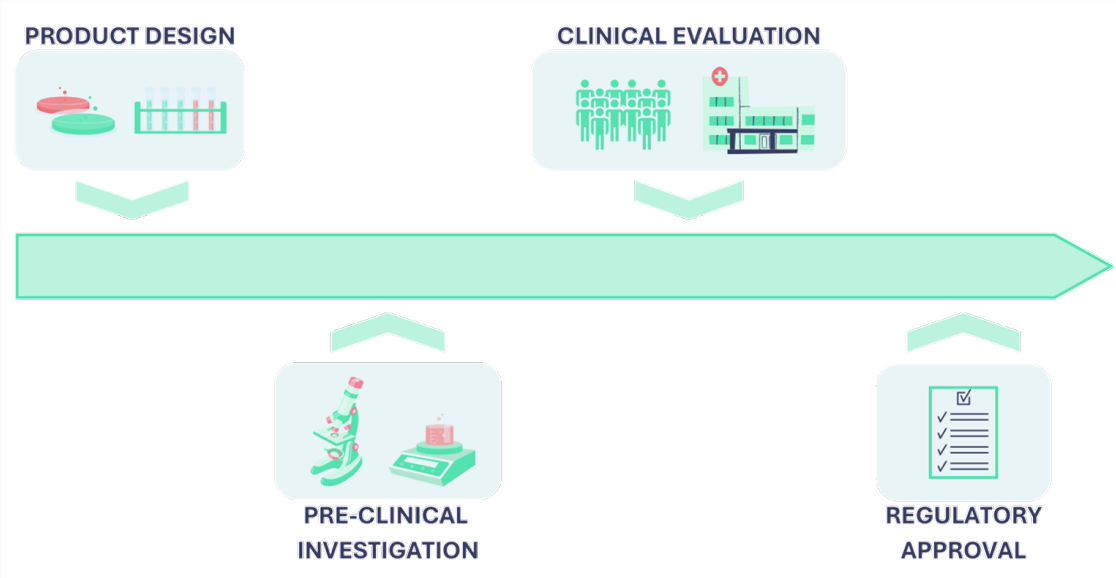

Figure 3: Main stages involved in the clinical translation of medical devices.

In the USA, 3D printed devices are regulated under Food, Drug and Cosmetics act (FD and C) which is implemented via device regulation 21 CFR (Code of Federal Regulations) and for quality system compliance by Part 820 in particular. The FDA's guidance on Technical Consideration for Additive Manufactured Medical Devices (2017) is important support to manufacturers.

The most common path in US for the high risk devices (Class II or III) based on the innovation platforms such as 3D printing and bioinks are, is approval through a Premarket Approval (PMA), whereas the 510(k) Pathway offers a faster route for devices demonstrating substantial

equivalence to an existing, approved device [8]. De Novo Pathway is fast approval for the lower to moderate-risk (Class I or II) innovative devices that lack a suitable predicate.

The Center for Devices and Radiological Health (CDRH) is responsible for the implementation of the FDA's CFR and oversees that patient and health providers have timely and continued access to safe, effective and high-quality medical devices. As part of providing this assurance, CDRH has been continuously supporting innovation in product development and manufacturing, with 3D printing being one of well-known most advanced technologies.

An overview of additive manufactured medical devices currently cleared under the 510(k) pathway, is presented in Table 1. In the US, most orthopaedic devices fall into Class II, which requires less stringent clinical data, and are therefore more commonly approved via 510(k). For lower-risk devices, the threshold for acceptable technological differences relative to the predicate may be lower, enabling greater flexibility in the interpretation of 'similarity' while maintaining assurance of safety and performance. However, the materials used in conventional additive manufacturing processes are less complex compared to ones used in 3D bioprinting, which incorporate living cells or biological components. To date, there are no records of 3D printed biological products in the FDA's De Novo, 510(k) or PMA database. Several combination products such as biologic-enhanced bone grafts used in orthopaedics (see Annex, Table 4) appear in the PMA database, but these differ substantially from 3D bioprinted constructs in both design and manufacturing complexity.

Table 1: Overview of medical devices, manufactured using additive manufacturing techniques, that have gained regulatory approval for market access through the FDA's 510(k) Approval Pathway. Devices were found in the FDA 510(k) database using search terms 'Additive Manufacturing' and '3D print'.

Search Term	Product & Company	Composition/Material	FDA Approvals
Dental Applications			
'Additive manufacturing'	Extra-oral, Additive Computer Aided Manufacture and Curing System *Deltamed GmbH*	e-Dent Temporary Resin and Extra-Oral Curing System	FDA 510(k) Premarket Approval Number: K102776 Decision Date: 02/18/2011 Class: Class II
'Additive manufacturing'	Additive Manufacturing Zirconia Customized Restoration *Hangzhou Thales Medtech Co., Ltd.*	Zirconia	FDA 510(k) Premarket Approval Number: K240586 Decision Date: 10/03/2024 Class: Class II
'Additive manufacturing'	Additively Manufactured Denture Resin *Aidite (Qinhuangdao) Technology Co., Ltd.*	Composed of acrylic resin, photo initiator, organic pigment and inorganic pigment. Additively Manufactured Denture Resin can be used in combination with a DLP 3D-printer utilizing wavelengths at 385nm or 405nm. A 3D-printer is not part of the device.	FDA 510(k) Premarket Approval Number: K242884 Decision Date: 11/22/2024 Class: Class II
'Additive manufacturing'	Additive Manufacturing (Light Curing) Crown Bridge Resin *Aidite (Qinhuangdao) Technology Co., Ltd.*	Methacrylic acid esters, inorganic filler, photoinitiator, organic pigments, inorganic pigments and additives	FDA 510(k) Premarket Approval Number: K250497 Decision Date: 04/30/2025 Class: Class II
'Additive manufacturing'	Additively Manufactured Aligner Resin *Aidite (Qinhuangdao) Technology Co., Ltd.*	Light-cured polyurethane resin	FDA 510(k) Premarket Approval Number: K251415 Decision Date: 08/27/2025 Class: Class II

‘3D print’	TruMatch CMF Titanium 3D Printed Implant System (Plates + Surgical Guides *Materialise NV*	Commercially pure titanium	FDA 510(k) Premarket Approval Number: K170272 + K173039 Decision Date: 08/08/2017 + 08/08/2018 Class: Class II
‘3D print’	AA temp temporary restoration 3D printing photoreactive resin *Enlighten Materials Co., Ltd.*	Methacrylate- based resin 3D printer is not included with the device.	FDA 510(k) Premarket Approval Number: K191590 Decision Date: 05/05/2020 Class: Class II
‘3D print’	BB Base 3D printing resin for denture base *Enlighten Materials Co., Ltd.*	Methacrylate- based resin 3D printer is not included with the device.	FDA 510(k) Premarket Approval Number: K191591 Decision Date: 08/18/2020 Class: Class II
Orthopaedic Applications			
‘Additive manufacturing’	BIOFOAM® Additive Manufacturing (BIOFOAM® AM), ADVANCE® BIOFOAM® Tibial Base, EVOLUTION® BIOFOAM® Tibial Base, DYNASTY® BIOFOAM® Acetabular Shell *Microport Orthopedics, Inc.*	Commercially Pure Titanium	FDA 510(k) Premarket Approval Number: K113271 Decision Date: 06/15/2017 Class: Class II
‘Additive manufacturing’	Prime and DYNASTY® Additive Manufacturing Shells *Microport Orthopedics, Inc.*	Titanium alloy (Ti-6Al-4V)	FDA 510(k) Premarket Approval Number: K202705 Decision Date: 08/20/2021 Class: Class II
‘3D print’	IMPIX 3D Print Cages (3D printed Lumbar cages) *Medicrea International SA*	Titanium Alloy (Ti-6Al-4V) according to the ASTM F3001	FDA 510(k) Premarket Approval Number: K163595 Decision Date: 11/13/2017 Class: Class II
‘3D print’	UNiD Patient Specific 3D printed cage (3D printed Lumbar cages) *Medicrea International SA*	Titanium Alloy (Ti-6Al-4V) according to ASTM F3001	FDA 510(k) Premarket Approval Number: K173782 Decision Date: 04/25/2018 Class: Class II
‘3D print’	Additive Orthopaedics Patient Specific 3D Printed Bone Segments *Additive Orthopaedics, LLC*	Medical Grade Titanium Alloy (Ti-6Al-4V) according to ASTM F3001	FDA 510(k) Premarket Approval Number: K180239 Decision Date: 05/16/2018 Class: Class II
‘3D print’	UNiD Patient specific 3D printed TLIF cage *Medicrea International SA*	Titanium Alloy (Ti-6Al-4V) according to the ASTM F3001.	FDA 510(k) Premarket Approval Number: K190092 Decision Date: 05/08/2019 Class: Class II
‘3D print’	MiRus 3D Printed Lumbar Interbody Fusion Systems consisting of the Callisto 3D Printed PLIF, HYPERION 3D Printed TLIF, CALYPSO 3D Printed LLIF, and ANTARES 3D Printed ALIF *MiRus, LLC*	Titanium alloy (Ti-6Al-4V ELI) per ASTM F3001-14	FDA 510(k) Premarket Approval Number: K191906 Decision Date: 05/18/2020 Class: Class II
‘3D print’	3D Printed PEEK Interbody System *Nvision Biomedical Technologies, Inc.*	PEEK OPTIMA™ LT1AMR5	FDA 510(k) Premarket Approval Number: K240250 Decision Date: 09/17/2024 Class: Class II
Radiology Applications			
‘3D print’	3D Bolus Software Application, 3D Brachy Software Application, Patient-Matched 3D Printed Radiation Therapy Accessory *Adaptiiv Medical Technologies Inc.*	Adaptiiv Medical Technologies Inc. solution is software as a medical device that consist of two (2) separate desktop applications: 1. 3D Bolus Software Application, which includes the Simple Bolus and Modulated Electron Bolus modules; 2. 3D Brachy Software Application, which includes the Surface Brachytherapy module. Accessories designed using 3D Bolus application are printed using: a. Polylactic Acid (PLA) filament b. Thermoplastic Polyurethane (TPU) filament c. Ultrasint® Thermoplastic polyurethane (TPU01) powder	FDA 510(k) Premarket Approval Number: K213438 Decision Date: 01/19/2022 Class: Class II

3.1.2. Advanced Therapy Medicinal Product (ATMP)

Bioinks that contain living human cells or tissues fall under the Advanced Therapy Medicinal Products (ATMPs) framework in the EU. ATMPs are defined by Regulation (EC) No 1394/2007 and are divided into somatic cell therapy medicinal products, tissue-engineered products, gene-therapy medicinal products and combined ATMPs.

A product is considered an ATMP when the cells or tissues have been substantially manipulated or are intended to carry out a different essential function in the recipient than in the donor. Substantial manipulation refers to modification of biological characteristics, physiological functions or structural properties relevant for clinical use, whereas processes such as cutting, centrifugation, antibiotic soaking or cryopreservation are not regarded as substantial manipulation. If a bioprinted product contains autologous cells that are not substantially manipulated and are used for the same essential function, it may be treated as a transplant under EU tissues and cells legislation rather than as an ATMP.

In the United States, bioprinted products are regulated under the framework for Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps). The FDA uses a risk-based approach: HCT/Ps that are minimally manipulated and intended for homologous use may be marketed under section 361 of the Public Health Service (PHS) Act with limited regulatory oversight. The FDA's regulations specify that such products are exempt from premarket approval if they meet four criteria: (i) minimal manipulation, (ii) homologous use, (iii) no combination with another article (other than water or standard preservatives) and (iv) limited systemic effects or autologous use. Products that do not meet these criteria are regulated as drugs, devices or biologics under section 351, requiring extensive premarket review, including demonstration of safety and efficacy and detailed information on manufacturing and quality-control practices. The concepts of minimal manipulation and homologous use differ slightly between structural tissues and cellular products; for structural tissues, minimal manipulation means processing that does not alter properties related to reconstruction, repair or replacement, whereas for cells or non-structural tissues it means processing that does not alter relevant biological characteristics.

Both, EU and US recognise that manipulation and intended use determine whether a bioprinted product is regulated as an advanced therapy or as a transplant. However, the EU and US frameworks are not fully harmonised. Recent reviews note that the proliferation of production and extraction sites for advanced therapies contributes to lack of harmonisation between international organisations, which may perform GMP evaluations at different stages of development and with different requirements [4], [5], [11].

Within the STRONG-UR fast-track approach, the device integrates multiple components: living Stromal Vascular Fraction (SVF) cells, a hydrogel platform (CuraDUO®) and a handheld bioprinter (BioPen). The combination of these biological and device-based elements means that the overall product may not fit neatly a single medical device category. Both EU and US regulatory authorities may therefore classify such products as a biologic-device combination

product and apply more stringent requirements than those imposed for ordinary 3D printed implants.

3.1.3. Combination product

Under the ATMP Regulation (EC No 1394/2007), any product that combines living cells with a structural scaffold often meets the definition of a tissue-engineered product. Where the construct is paired with a medical device component (e.g. a hydrogel scaffold, 3D printing unit), EU guidance distinguishes between:

- Combined ATMPs – the cell component is primary; the scaffold or printing unit is ancillary. These products must comply with both ATMP requirements and device-specific standards.
- Combination products – the device component provides the PMOA; the cell component is secondary. These still trigger dual regulation because the biologic part must meet ATMP standards while the device must satisfy the MDR.

Given that the STRONG-UR fast-track device relies on living cells to achieve its intended therapeutic effect, it is likely to be classified as a combined ATMP. Such a classification subjects the product to a rigorous regulatory oversight process: manufacturers must obtain a marketing authorization through the EMA, implement a comprehensive QMS system, and ensure compliance with both ATMP and medical device requirements.

In the United States, the FDA regulates human-cell and tissue products under a tiered system. Section 361 of the PHS Act allows “HCT/Ps” to be marketed without premarket approval if they are minimally manipulated, intended for homologous use, not combined with other active components and have no systemic effect or are autologous. Once cells are mixed with a hydrogel scaffold and printed on demand, they usually no longer meet these conditions. Products that fail any of the section 361 criteria are regulated under section 351 of the PHS Act as biological products – meaning they require an Investigational New Drug application and a Biologics License Application, including full pre-clinical/clinical data and detailed information on manufacturing controls.

Therefore, a POC 3D printed device comprising viable cells and a hydrogel would not be considered a “361 HCT/P”. Instead, the FDA would likely view it as a combination product (biologic plus device) regulated under section 351, meaning it must comply with both biologics requirements and medical device quality system regulations.

Across both jurisdictions, combining living cells with a hydrogel and a 3D printing unit elevates the product into the most stringent regulatory categories, far beyond the simplified pathways available for low-risk CMDs. Likewise, the absence of harmonised standards governing the integration of hydrogels and cells into bioinks, as well as the bioprinting process itself, remains a major barrier to regulatory approval and clinical translation.

4. GMP and CMC requirements

Good manufacturing practice (GMP) and Chemistry, Manufacturing, and Controls (CMC) documentation ensures batch consistency, safety, and reproducibility. In the context of bioinks and bioprinting, this encompasses all stages, from raw material considerations, such as cell sourcing, GMP compliant expansion, and polymer origin, to process parameters including sterilisation methods, printing conditions, and final construct geometry. While the versatility and tunability of bioinks are among the most attractive features of bioprinting, this same flexibility presents challenges both in establishing specific guidelines and in achieving compliance with current, broadly defined GMP standards. This highlights the need for researchers and developers to integrate regulatory and manufacturing considerations early in product development, supported by a QMS system aligned with applicable standards. Implementation of a QMS system conforming to applicable standards is a mandatory component of the regulatory approval process. Some of the key considerations for GMP development of bioprinted products are discussed in this section.

4.1. Key GMP Requirements for Bioink Materials

As mentioned above, bioink materials intended for clinical use must be developed, sourced, characterised, controlled, and documented in accordance with GMP principles to ensure product safety, quality, and consistency.

4.1.1. Raw Material Qualification and Traceability

Raw material quality and traceability are essential for GMP compliant manufacturing. A central element is supplier qualification, supported by a documented supplier-management system. This includes reviewing supplier quality certifications, performing on-site audits when needed, and maintaining an updated approved-supplier list. Any change in supplier, manufacturing site, or material specifications must be evaluated through formal change control to assess potential impact on product quality and compliance.

Biomaterial-related Raw Material Qualifications and Traceability

The biomaterial component of bioinks may consist of synthetic components (e.g., polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), photo-initiators) and biological components (e.g., decellularized matrix derivatives, collagen, hyaluronic acid). Synthetic materials require verification of chemical identity and purity, as well as batch-to-batch consistency. Biological materials require additional controls, including screening for transmissible agents, viral and microbiological safety, and validated processes to minimize contamination. Their origin must be documented and, when relevant, aligned with applicable pharmacopeial or regulatory requirements.

Robust material specifications must be established for each raw material, defining acceptance criteria such as purity, molecular weight, viscosity, particle size, or microbiological limits.

Certificates of Analysis (CoA) must be reviewed, and critical materials require independent confirmatory testing. Approved materials must have defined storage conditions and retest/re-evaluation periods.

Cell-related Raw Material Qualifications and Traceability

For the cellular component of bioinks, raw material qualification and traceability are principal GMP controls. ISO 13485:2016 is used to manage purchasing, supplier qualification, batch records, and change control to ensure all cell contact materials, ranging from cell culture media, polymers, photoinitiations to cell-processing reagents (e.g. enzymatic-based cell-detachment solutions), meet predefined specifications and acceptance criteria [12]. Additionally, ASTM F202725 provides guidance for defining and verifying starting material specifications for tissue-engineered medical products, while explicitly recognising that starting-material variability can shift cell behaviour and downstream performance [13].

Cell-source qualification requires stricter oversight than non-cellular materials. For primary human cells, procurement must be ethical and fully traceable, with donor eligibility assessed according to 21 CFR Part 1271. EU requirements are defined under the EU Tissues and Cells framework (Directive 2004/23/EC) and EMA expectations for ATMP clinical programs. For iPSC-derived materials, identity, genetic stability, and consistency (e.g., banking strategy, drift controls, and comparability) must be justified according to cell-substrate principles [14].

To limit cell drift risks, a two-tier banking system (Master Cell Bank (MCB) to Working Cell Bank (WCB)) should be used, with validated ultra-low-temperature storage, controlled thaw/handling, and defined WCB passage windows, and each manufacturing run linked to a specific WCB/lot [14]. Full chain-of-identity and chain-of-custody records are required from donor to final batch, and electronic systems should follow FDA Part 11 guidance. The ISBT 128 standard can be used to standardize traceability and prevent mix-ups across processes [15].

Overall, traceability is essential at every stage of the bioink manufacturing process. This includes full batch traceability, clear linkage to supplier batch numbers, and comprehensive documentation within manufacturing batch records. Such traceability is critical for effective investigations, product recalls, and maintaining regulatory compliance.

4.1.2. Material Characterisation and Safety

Comprehensive characterization of bioink materials is essential to demonstrate their suitability for GMP compliant manufacturing and their intended clinical application. Such characterization must encompass physicochemical properties, biological safety, and performance-related attributes to ensure consistent quality, safety, and functionality throughout the product lifecycle.

Physicochemical Characterisation

Physicochemical analysis of bioinks typically includes confirmation of chemical structure (e.g. Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR)) and evaluation of molecular weight (e.g. Gel Permeation Chromatography (GPC)). Key functional

parameters, often defined as critical quality attributes (CQA), such as rheology, gelation kinetics, crosslinking efficiency, swelling behaviour, and mechanical properties must be clearly specified and controlled. Physicochemical testing not only establishes the CQAs required for in-process control; it is also imperative for assessing how these characteristics influence the cellular components of the bioink, as for example mechanical stresses during extrusion can damage cells.

Residual solvents, unreacted monomers, and photoinitiators must be quantified and demonstrated to remain below acceptable limits. These safety-relevant constituents require extractables and leachables testing, along with toxicological justification based on literature data and permitted daily exposure (PDE) calculations.

Printability is evaluated to determine how closely printed structures replicate the intended geometry. Assessments can include simple filament-based tests (uniformity ratio, spreading ratio, printability index) as well as basic self-support assays, which are particularly relevant for viscoelastic and softer materials such as hydrogels. Examples include printing across spaced pillars to quantify filament collapse or depositing multiple layers to evaluate whether the construct maintains structural integrity.

As the field matures, standardized guidelines are needed to align rheological measurements with practical printability metrics. Oscillatory rheology is a highly sensitive technique commonly used to measure hydrogel viscoelasticity before and after crosslinking. Dynamic mechanical measurements are required to separate elastic and viscous contributions to the modulus. Additionally, there is growing interest in how hydrogel viscoelasticity and relaxation time influence cell behaviour, both on the surface and within the matrix [8].

Biocompatibility and degradation behaviour

Biocompatibility is a fundamental safety requirement. Biocompatibility evaluation should align with ISO 10993 principles, which define the extent of testing based on the product's intended use and associated risk profile. This evaluation may include cytotoxicity testing, sensitisation and irritation assessments, genotoxicity (where relevant), carcinogenicity, hemocompatibility (if applicable), and implantation studies for *in vivo* applications. Testing strategies must be developed using a risk-based approach and take into account the intended clinical use, duration of exposure and degradation profile of the materials.

The latter is particularly important for biodegradable bioinks. Their degradation behaviour must be fully characterized in line with ISO 10993-9, including identification and quantification of degradation products, degradation kinetics under physiological conditions, their impact on pH and the local environment, and the expected clearance mechanisms. Such information is required to ensure that degradation products do not pose toxicological risks and that the degradation profile aligns with the intended therapeutic or structural function [16].

Sterility and Microbiological Control

Regardless of the sterilization strategy employed, the resulting sterility must be verified through bioburden testing and endotoxin assessment. Sterility assurance levels (SAL) must be achieved

without compromising the critical material properties of the bioink. Appropriate controls must be implemented to ensure that the selected sterilization method is compatible with both the material and any living cells introduced post-sterilisation, and does not adversely affect safety, functionality, or performance.

Because many bioinks are heat-labile, they cannot undergo terminal steam sterilization. In practice, sterile filtration (when feasible) and aseptic processing or assembly are therefore commonly used, consistent with ISO 13408-1:2023 principles for aseptic processing [17].

Endotoxin contamination should be controlled and quantified using the Limulus Amebocyte Lysate (LAL) assay according to USP <85>. For cell-containing or cell-contacting applications, endotoxin limits are often set conservatively (e.g., below 0.5 EU/mL) to minimise the risk of inflammatory or immunogenic responses in sensitive biological systems. Furthermore, every agent, device and/or compound which interacts with the cells during the manufacturing process must be tested for endotoxin presence or has to possess low-endotoxin certification from the supplier.

4.1.3. Other considerations

A compliant QMS system must include quality control and release testing, stability and storage requirements, and comprehensive quality management and documentation. The requirements for compliance are defined in ISO 13485:2016 and 21 CFR Part 820. While these requirements can be challenging to implement for bioinks, due to their inherent biological variability and the integration of living cells, they fall outside the scope of this report and will not be addressed in further detail.

4.2. Key GMP Requirements for 3D-Printing Process

GMP compliance of 3D printing processes requires defined and controlled manufacturing conditions to ensure reproducibility, product quality, and patient safety. Due to the complexity of bioprinting systems, control must extend across materials, process parameters, equipment, and digital workflows.

4.2.1. Processes and parameter control

Critical process parameters (CPPs) for 3D printing, including printing conditions, crosslinking methods, and post-processing steps, must be defined, validated, and maintained within controlled ranges. These parameters directly influence CQAs such as structural integrity, resolution, mechanical performance, and product homogeneity. A non-exhaustive overview of potential quality risks associated with different printing techniques is provided in Annex, Table 5. The 3D printing process should be maintained in a well-defined state of control through standardized procedures, in-process monitoring, and predefined acceptance criteria. Potential sources of variability, including equipment, software, and process parameter fluctuations, must be understood and minimized using a risk-based approach.

Robust control strategies should be established for critical aspects applicable across 3D printing technologies, including equipment design, product orientation, layer thickness, print head positioning, printing speed, and printing patterns. During process development, critical process attributes and acceptable operating ranges must be identified and justified, with quality systems enabling timely detection of deviations and implementation of corrective actions. Monitoring frequencies should be appropriate with respect to the technology, process duration, material residence time, and associated risk, supported by comprehensive risk assessment, suitable sampling strategies, and quality control procedures to detect and reject non-conforming materials [18].

Raw Material and Intermediate Control

3D printing processes require stringent control of raw materials, as material characteristics can directly influence CQAs, particularly given the layer-by-layer nature of fabrication and the potential for physical and chemical transformations during processing. Both primary raw materials and any inactive ingredients introduced throughout the printing process may affect final product quality, with material requirements varying substantially across different 3D printing technologies. Inadequate material characterization, for example insufficient control of flow or micromeritic properties in powder-based processes, can lead to non-uniform layer deposition, poor interlayer adhesion, and deviations from the intended product design. Consequently, close collaboration with raw material suppliers, control of lot-to-lot variability, and well-defined incoming material specifications supported by validated analytical methods are essential. Key material attributes influencing printing performance include particle size distribution, flow behaviour, thermal and rheological properties, impurity profiles, and degradation behaviour, all of which have a direct impact on printing precision and product quality [18].

To mitigate the cumulative effects of material changes during processing, the impact of the printing process and environmental conditions on raw materials must be systematically evaluated. Based on these assessments, limits on material reuse cycles should be established and justified through process validation to ensure continued compliance with predefined quality requirements [19]. Overall, robust control of raw materials and intermediates is a fundamental prerequisite for ensuring consistent product quality, GMP compliance, and regulatory conformity in 3D printing-based manufacturing environment [20].

Control of the Printing Device

Installation and operational verification are essential to ensure that 3D printing equipment is correctly installed, functions as intended and reliably supports product quality. Verification activities should confirm proper installation and integration of all critical components and supporting infrastructure, including safety-relevant systems. The equipment must demonstrate stable start-up and operation, with performance assessed under normal as well as boundary or extreme operating conditions to confirm reliable functionality across the full range of anticipated process settings.

Performance verification should focus on quality-relevant outputs such as printing accuracy, surface quality, microstructure, and mechanical properties, taking into account the inherent anisotropy of additively manufactured products by assessing performance in different build directions (X-Y versus X-Z direction). Understanding the relationship between printing parameters and product quality is critical; therefore, optimal parameters for the intended use must be identified and validated for each printing technology. Once validated, key parameters must be strictly controlled during routine production, and any changes to critical settings should trigger revalidation to ensure continued compliance with predefined acceptance criteria [19].

Control of Printed Structure

Control of the printed structure focuses on verifying that dimensional accuracy, surface quality, internal integrity, chemical composition, and mechanical performance meet predefined requirements. Depending on the application, printing accuracy evaluation may involve visual inspection, dimensional measurements, microscopy, surface roughness analysis, and non-destructive techniques such as X-ray-based methods (e.g. micro-CT) or ultrasonic testing, particularly for complex or porous internal structures. Surface quality and dimensional accuracy are strongly influenced by build orientation and support design and must therefore be addressed during process development.

Chemical composition and mechanical properties should be assessed using established, standardized analytical and test methods appropriate to the intended use. Mechanical testing typically includes strength, ductility, and hardness measurements performed on standardized test specimens. These assessments are generally conducted during equipment qualification and process validation to demonstrate that printed products meet defined quality and performance criteria [19].

Equipment and Software Workflow

3D printing relies on a software-driven workflow, making software control a critical aspect of both process development and routine manufacturing. Alignment between digital design and manufacturing execution is essential, with clinically or functionally relevant design parameters clearly defined and controlled within justified ranges in the software environment. Increasing design complexity introduces risks related to file handling, data transfer, and format conversion, which must be carefully managed.

Once finalized, design files should be archived and maintained under controlled conditions using standardized file formats to ensure data integrity and reproducibility. The Additive Manufacturing File (AMF) format defined in ISO/ASTM 52915 is an example of an appropriate standard for managing finalized design files [21].

Scale up considerations in 3D printing

Scale-up in 3D printing presents unique challenges due to limited industrial maturity and the strong dependence of product quality on equipment-specific and process-specific settings. During research and pilot-scale development, structured experimental studies should be

performed to identify process variables that significantly influence product quality and performance, thereby supporting the identification of CPPs.

Scale-up impacts vary by technology: extrusion-based systems with multiple identical print heads may show limited variability, whereas changes in nozzle design, print head configuration, or operational principles between pilot and commercial equipment often require parameter re-evaluation. Inkjet-based systems may require recalibration of print head geometry and operating conditions following equipment modifications. Additional considerations include powder handling, material reuse, base plate layout, feed rates, and post-processing conditions. Many scale-up risks can be mitigated through real-time monitoring of established physicochemical parameters within validated operating ranges to ensure consistent quality during expanded production.

4.2.2. Process Validation Considerations

Process qualification is the first stage of 3D printing process validation and demonstrates that the process is capable of producing products that meet predefined quality requirements. It includes identification of CPPs, capability studies, and preparation of validation documentation, beginning with the definition of critical equipment, utilities, process steps, acceptance criteria, and responsibilities [22].

Validation is conducted through Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) to confirm correct operation under defined conditions (Figure 4, Table 2). Test schedules and procedures must be approved in advance, and qualification activities must confirm that facilities, utilities, and supporting systems are properly designed and implemented. Together, equipment qualification and process validation provide documented evidence that the manufacturing system can reliably produce safe, specification-compliant medical devices of consistent quality [23].

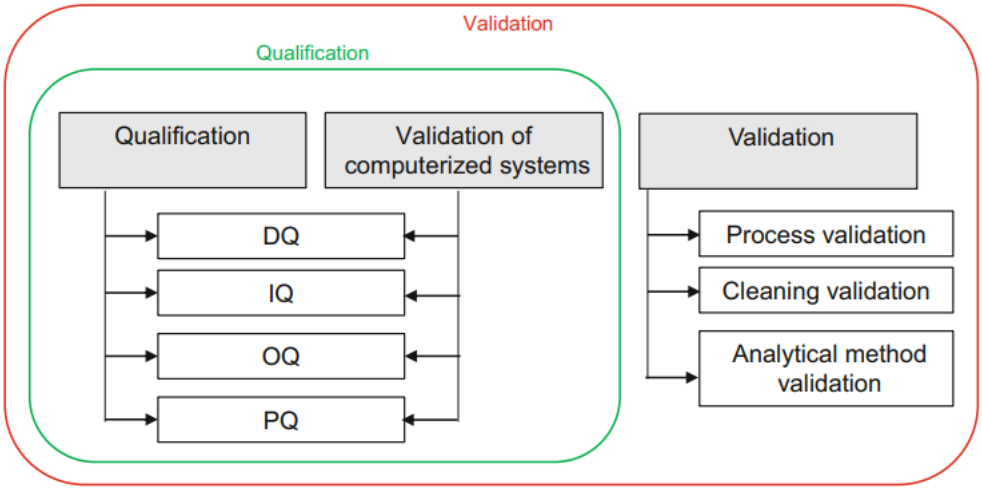

Figure 4: Relationship Between Qualification and Validation, Including Qualification and Validation of Computerized Systems (DQ: design qualification, IQ: Installation qualification, OQ: Operational qualification, PQ: Performance qualification) [23].

Table 2: Validation Lifecycle Framework

Stage	Name	Scope	Reference
1. URS	User Requirement Specification	Functional, operational, safety, and regulatory requirements. CPP ranges, environmental specs, software requirements, data integrity, intended use.	ICH Q8(R2); ISO 13485 §7.3; GAMP 5
2. DQ	Design Qualification	Verification that proposed design satisfies all URS requirements before procurement. Vendor documentation, component specs, biocompatibility of wetted parts, safety features.	ISO 13485 §7.3.5; EU MDR Annex I
3. IQ	Installation Qualification	Verification of correct installation per design spec and manufacturer recommendations. Utilities, environment, calibration certificates, software version.	EU GMP Annex 15 §8; 21 CFR 820.70(g)
4. OQ	Operational Qualification	Testing across full CPP range including worst-case boundary conditions. Alarm and interlock verification. Software functional testing.	EU GMP Annex 15 §9; 21 CFR 820.70; ISO/ASTM 52920
5. PQ	Performance Qualification	Min. 3 consecutive production-scale runs demonstrating all CQAs met. Statistical process control data generated. Uses qualified bioink materials.	EU GMP Annex 15 §10; FDA PV Guidance; ICH Q8(R2)

5. Overview of Applicable Guidelines

The regulatory framework governing medical devices and emerging bioprinting technologies is inherently complex and multidisciplinary, reflecting the diverse biological, engineering, and manufacturing principles underpinning these products. Bioprinting processes frequently intersect with established regulatory domains, most notably those pertaining to medical devices, ATMPs, combination products, and pharmaceutical manufacturing quality systems. Consequently, compliance requires the integration of standards and guidelines originating from multiple international bodies.

Table 3, presented below, summarises a selection of influential regulatory documents and standards issued by organisations such as the International Organization for Standardization (ISO), the International Council for Harmonisation (ICH), ATMP regulatory authorities, American Society for Testing and Materials (ASTM), GMP frameworks, and CMC guidance relevant to medical devices, ATMPs and combination products. While not exhaustive, this compilation highlights core references that are most frequently applicable to the development, characterisation, and manufacture of 3D printed and bioprinted constructs and processes within a regulated environment. Collectively, these cross-sectoral standards illustrate the growing need for guidance and standardisation specifically tailored to 3D bioprinting products and processes, that can support regulatory compliance, facilitate clinical translation, and uphold patient safety.

Table 3: Overview of applicable guidelines for current regulatory framework

Guideline	Title	Topic/Extra Info
Safety/Risk Management		
ISO 14971:2019	Medical devices — Application of risk management to medical devices	Risk Management
ISO/TR 24971:2020	Guidance on the application of ISO 14971	
ISPE GAMP 5 Guide	A Risk-Based Approach to Compliant GxP Computerized Systems	
Product-based Guidelines		
ISO 10993 series	Biological evaluation of medical devices	Biocompatibility
(FDA) 21 CFR Part 1271	Human cells, Tissues, and cellular and tissue-based products (HCT/P's)	Regulation
ISO 22442-1:2020	Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management	Raw materials from natural origin
ISO 22442-3:2007	Medical devices utilizing animal tissues and their derivatives – Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents	

ASTM F2027-25	Standard Guide for Characterization and Testing of Raw or Starting Materials for Tissue-Engineered Medical Products	
ASTM F2212-20	Standard Guide for Characterization of Type I Collagen as Starting Materials for Surgical Implants and Substrates for Tissue-Engineered Medical Products (TEMPs)	
ICH Q3C(R8)	Impurities: Guideline for Residual Solvents	
ICHQ5A(R2)	Guideline on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin	
ASTM F3659-24	Standard Guide for Bioinks Used in Bioprinting	
Process-based Guidelines		
ISO/ASTM 52915:2020	Specification for additive manufacturing file format (AMF)	
ICH Q8(R2)	Pharmaceutical development	
ISO/ASTM 52900:2021	Additive manufacturing – General principles – Fundamentals and vocabulary	
ISO/ASTM 52920:2023	Additive manufacturing – Qualification principles – Requirements for industrial additive manufacturing processes and production sites	
ISO/ASTM 52904:2024	Additive manufacturing of metals – Process characteristics and performance – Metal powder bed fusion process to meet critical applications	
ISO/ASTM 52902:2023	Additive manufacturing – Test artefacts – Geometric capability assessment of additive manufacturing systems	
ISO 14644-1:2015 ISO 14644-3:2019	Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration - Part 3: Test methods	
IEC 62304:2006	International Electrotechnical Commission (IEC): Medical device software – Software life cycle processes	
FDA Process Validation Guidance	Guidance for Industry Process Validation: General Principles and Practices	
ISO 13408-1:2023	Aseptic processing of health care products – Part 1: General requirements	
Clinical Evaluation		
ISO 14155:2020	Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice	
GMP and CMC requirements		
ISO 13485:2016	Quality Management Systems (QMS) for Medical Devices	QMS for Medical Devices
(FDA) 21 CFR Part 820	Quality Management System (QMS) Regulation	QMS for Medical Devices
ISBT 128	Standard for Coding Medical Products of Human Origin	

(FDA) 21 CFR Part 11	Electronic Records; Electronic Signatures
EU GMP Annex 1	Manufacture of Sterile Medicinal Products
EU GMP Annex 11	EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 11: Computerised systems
EU GMP Annex 15	EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use – Annex 15: Qualification and Validation
ICH Q10	Pharmaceutical quality system (PQS)
ISO 14937:2009	Sterilization of health care products. General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices
Post-Market Surveillance	
ISO/TR 20416:2020	Medical devices – Post-market surveillance for manufacturers

6. Regulatory Challenges Specific to Bioprinted Products

Innovative 3D bioprinted products comprise a diverse range of components and are manufactured using an equally broad array of fabrication techniques, therefore mapping their regulatory pathway is inherently challenging. The key challenges associated with defining this pathway are outlined below.

Classification

The classification of products places them into distinct regulatory siloes, as described by *Nielsen et al.* [11]. Combination products, which incorporate both biologics and components that may be considered medical devices, must be evaluated on a case-by-case basis to determine their PMOA. This assessment defines which regulatory guidelines could be applicable. Because 3D bioprinted products inherently possess a highly complex architecture of integrated components, they often do not align well with the current regulatory framework, which was primarily designed for standardized, mass-manufactured products rather than patient-specific, innovative constructs [5], [11], [24].

Quality and safety aspects

The purpose of the regulatory framework is to ensure patient safety and product efficacy. To achieve this, both medical devices and pharmaceuticals undergo extensive characterization prior to market access. However, the absence of established standards and guidelines for 3D bioprinted products poses significant challenges in ensuring consistent, reliable assessments of their safety and quality. Many characterization methods currently used in biomedical product evaluation are destructive in nature, making them unsuitable for patient-specific 3D printed constructs where only a single, individualized product is manufactured [5], [11], [24].

Additionally, sterility remains a critical requirement. Yet standardized sterilization methods, such as ethylene oxide treatment or gamma irradiation, are often incompatible with the biomaterials used in bioinks, which may degrade, undergo alteration of physiochemical characteristics or lose functionality under such conditions [5], [8]. Quality control must also extend beyond the final product; it must encompass the entire manufacturing workflow. Every tool interacting with the material downstream of sterilization, including the bioprinter, must be fully sterilized. Furthermore, both in-line and off-line quality control strategies must be defined [6]. Collectively, these factors introduce substantial challenges for establishing GMP frameworks suitable for the clinical translation of bioprinted products.

GMP development is further complicated by the decentralized nature of bioprinting workflows. Key components of the final construct are often sourced from, or developed by, different specialized stakeholders. This dispersion of responsibilities introduces uncertainties regarding liability and accountability [5], [8], [11], [24], [25]. Another issue concerns the scope of the combination product: does it encompass only the biological construct, or also the software and bioprinter used in its development? Regulatory requirements for these auxiliary

components become significantly more stringent if they are deemed part of the finished product [5], [11], [24], [25].

Product- vs process-based approach

Overall, current regulations rely on risk assessment and risk management principles. For 3D bioprinted constructs, however, the risk profile remains largely unknown [5], [11], [24]. The existing regulatory focus is also highly product- and application-specific. A shift toward a process-based regulatory approach may better accommodate patient-specific therapies and the diversity of materials used in regenerative medicine [5], [11]. If the safety of the manufacturing process can be demonstrated, overall risk could be substantially reduced. Yet this approach requires the development of new standards that define acceptable methods for proving process safety. The creation of such standards often lags behind technological innovation, making harmonization difficult. Moreover, a process-based framework introduces the risk of constraining innovation in bioprinting technologies as manufacturers strive to maintain process compliance [11].

7. Practical Pathways & Recommendations

In this report, the current regulatory frameworks are applied to the STRONG-UR project, to propose a suitable regulatory pathway for its innovative bioprinting-based approach to regenerate urethral defects. The focus is on the STRONG-UR single stage or fast-track approach (Figure 5), which addresses the repair of a unilateral urethral defect. In this procedure, SVF cells are harvested from autologous adipose tissue and combined with a hydrogel ink formulated using 4Tissue's CuraDUO platform to create a bioink. The defect is subsequently treated *in situ* using this bioink and the AdBioInk BioPen system.

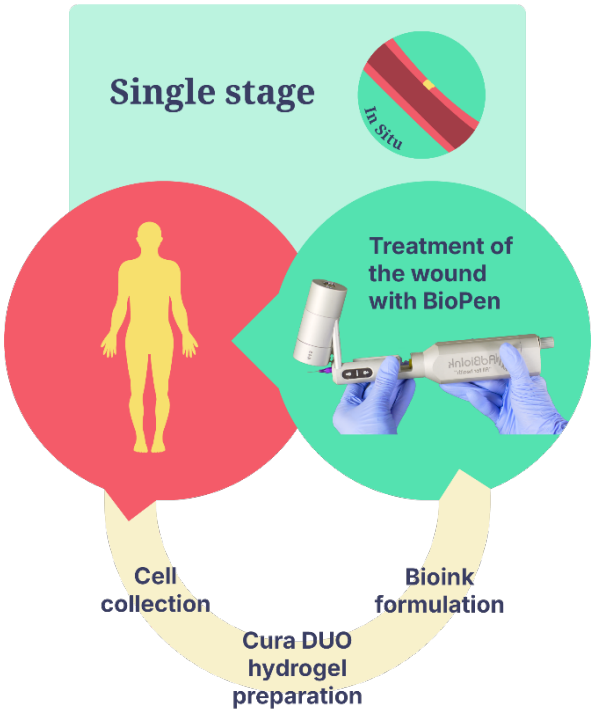

Figure 5: STRONG-UR's single stage – fast-track approach [1] .

In this context, the product consists of a bioprinted construct that integrates a hydrogel scaffold with living cells. Similar to other bioinks, such a construct is classified as a combination product because it includes both biological components (SVF cells) and medical device components (hydrogel, BioPen).

Under the current regulatory framework, the key question is whether the PMOA of the combination product is driven by the device component or by the cellular/tissue component. If the PMOA is device-driven, the product falls under Article 1(8) of the MDR. If the cellular component is considered primary, both the ATMP Regulation (Article 6) and MDR requirements apply. This approach is complex because it must account for several elements simultaneously: the biological cells, the biomaterial ink, the BioPen delivery device, and the *in situ* bioprinting method.

A potential alternative for the STRONG-UR product could be the 'custom-made' exemption under the MDR or the 'hospital exemption' under the ATMP Regulation (Article 28, Regulation 1394/2007). The custom-made exemption is intended for patient-specific devices used in unusual or non-routine circumstances, particularly when they are not intended for industrial scale manufacturing or mass distribution [5], [8], [11], [24], [25]. Article 2(3) of the MDR exempts manufacturers from some of the more stringent regulatory requirements, provided these individualized devices are not generally placed on the market. This exemption has been used to approve several patient-specific 3D printed orthopaedic implants. While this pathway may offer opportunities for the STRONG-UR application, it is unlikely to serve as a general route for all 3D bioprinted products, given the ambiguity surrounding terms like "mass-produced" or "industrial manufacturing processes". In addition, concerns have been raised about whether this exemption is appropriate for high risk bioprinted products [5], [8], [11], [25].

A third, and arguably the most suitable, regulatory pathway for the STRONG-UR fast-track approach POC manufacturing [5], [6], [7], [8]. In this approach, the product is manufactured directly within the healthcare institution. Several custom-made 3D printed medical devices have already been produced through POC manufacturing, especially in surgical fields such as trauma care and orthopaedic oncology, where rapid production is advantageous. Given the *in situ* bioprinting nature of the STRONG-UR fast-track procedure, POC manufacture appears to be the best fit. However, POC manufacturing also introduces uncertainties, particularly concerning the assignment of manufacturer liability. In a POC model, the hospital or healthcare facility may be considered the manufacturer and thus subject to stringent regulatory obligations typically imposed on industry [5], [8], [25]. An alternative regulatory concept addressing this challenge has been considered by the Therapeutic Goods Administration (TGA) in Australia. Their framework for Medical Device Production Systems (MDPS) suggests a shift of regulation from the final product to the manufacturing process itself, allowing healthcare facilities to produce devices without undergoing the full set of assessments required for traditional manufacturers [7], [8].

8. Conclusion

Innovative 3D bioprinting technologies hold substantial potential to advance and transform current medical practice, particularly using regenerative medicine and tissue engineering strategies. However, this potential can only be realised once these technologies are successfully integrated into clinically compliant and regulated workflow. The novelty and complexity of 3D bioprinted products pose significant challenges to the existing regulatory framework. Complexity arises from the breadth of new biomaterials used in bioinks, the diversity of components involved (biologics, biomaterials, bioprinting hardware), and the wide range of additive manufacturing techniques (e.g. selective laser sintering (SLS), extrusion, digital light processing (DLP)). These technological possibilities support innovation, yet they simultaneously introduce considerable uncertainty, especially with respect to risk. New materials, new processes, and, most importantly, new combinations of components may introduce unpredictable interactions affecting safety and performance. While individual components may fit within current regulations, their integration into a single system creates exponentially greater regulatory complexity.

In addition to their technical complexity, bioprinting technologies often involve decentralised or distributed manufacturing models. This raises questions regarding the implementation of standardisation requirements, such as QMS systems, and introduces unclear allocation of regulatory liability and accountability. Furthermore, the regulatory scope of the device must be clearly defined. For example, the regulatory scope for bioprinters is not yet clearly defined and requires further clarification when only the final bioprinted construct comes into contact with patients.

Some authors have proposed shifting from a product-based to a process-based regulatory approach. This aligns with the Australian framework for MDPS, which redirects regulatory oversight from the final device to the manufacturing system itself. Such an approach could allow healthcare facilities to produce devices without undergoing the full suite of assessments typically required for traditional manufacturers.

These challenges underscore not only the disruptive nature of bioprinting but also the urgent need for new, adaptive regulatory and standardisation strategies. Efforts are already underway to raise awareness, identify priorities, and bring together relevant stakeholders. Nonetheless, substantial work remains, and progress will require an open minded perspective that is willing to evolve beyond existing frameworks.

For the STRONG-UR fast-track system, several regulatory pathways within the current framework have been considered: the ‘custom-made’ exemption under the MDR or the ‘hospital exemption’ under the ATMP Regulation (Article 28, Regulation 1394/2007). However, given the high-risk nature of bioprinting, the feasibility of these options remains uncertain. The most plausible pathway is POC manufacturing, whereby the product is manufactured directly within the healthcare institution, either by the institution itself or by a contracted manufacturer

operating in or near the facility. Yet, POC manufacturing also brings uncertainty regarding the assignment of manufacturer liability. In such a model, the hospital may be considered the legal manufacturer and therefore subject to regulatory obligations typically imposed on industry.

Overall, these considerations highlight the need for regulatory and standardisation initiatives that support a balanced evolution of the framework; one that minimises risk, ensures patient safety, and supports innovation.

In conclusion, this deliverable defines the regulatory context for the STRONG-UR project and identifies key points at which GMP-related requirements are anticipated during product development. It serves as a structured foundation for subsequent activities, while detailed GMP implementation elements are addressed in later project deliverables.

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Annexes

Table 4: Overview of combination products (medical device + biologic) that have received regulatory approval through the FDA's Premarket Approval (PMA) pathway. Devices were identified in the FDA PMA database by filtering for the following categories: "Advisory Committee: Orthopaedic" and "Combination Product". Only devices with decision dates from 2002 onward were included.

Product & Company	Description	Composition/Material	PMA info
Orthopaedic Applications			
PearlMatrix™ Bone Graft *Cerapedics, Inc.*	PearlMatrix™ P-15 Peptide Enhanced Bone Graft	PearlMatrix™ Bone Graft is a composite bone graft material consisting of a synthetic **peptide (P-15)** found naturally occurring in human Type I collagen, adsorbed onto **calcium phosphate particles**, which are incorporated into a bovine collagen matrix as an inert carrier. Calcium phosphate particles: - porcine anorganic bone mineral (pABM) - provide a scaffolding & source of calcium for new bone growth Synthetic collagen fragment (P-15): - short chain 15 amino acid peptide - mimics a cell binding domain of human Type I collagen - more favourable environment: facilitates cell attachment	Number: P240001 Approval Date: June 18, 2025 Class III
i-FACTOR™ Peptide Enhanced Bone Graft *Cerapedics, Inc.*	i-FACTOR™ Peptide Enhanced Bone Graft (also referred to as i-FACTOR™ Bone Graft or i-FACTOR™ Putty) is a composite bone graft material consisting of multiple components: (i) a synthetic peptide (P-15) adsorbed onto (ii) calcium phosphate particles, which are suspended in (iii) a hydrogel carrier.	P-15 peptide component: - short chain peptide consisting of 15 amino acids that mimics the sequence of amino acids found in residues 766-780 of the α1 chain of Type I collagen according to the following sequence: Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val Calcium phosphate granule component: - anorganic bone mineral (ABM) / hydroxyapatite granules derived from bovine bone Hydrogel component: plant-derived sodium carboxymethycellulose (NaCMC) in combination with glycerin and water	Number: P140019 Approval Date: November 3, 2015 Class III
Augment® Bone Graft *Wright Medical Technology, Inc.*	Augment® Bone Graft combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable synthetic bone matrix (beta-tricalcium phosphate or β-TCP).	These two components are packaged together and are physically combined immediately prior to use as follows: - 1.5, 3, 6, or 9cc of synthetic β-TCP in granule form (nominal particle size 1 to 2 mm) 1.5, 3, 6, or 9 mL of rhPDGF-BB (0.3 mg/mL in 20mM USP sodium acetate buffer, pH 6.0)	Number: P100006 Approval Date: September 1, 2015 Class III
Nuflexxa (I% Sodium Hyaluronate) *Ferring Pharmaceuticals, Inc.*	Nuflexxa consists of a one percent bacteria-derived sodium hyaluronate solution in phosphate buffered saline.	Hyaluronic acid is composed of alternating D-glucuronate and N-acetylglucosamine residues, linked in alternating~ (1→4) and (1→3) bonds. Each 1mL of Nuflexxa contains: - Sodium hyaluronate: 10 mg - Sodium chloride: 8.5 mg - Disodium hydrogen phosphate dodecahydrate: 0.56 mg - Sodium dihydrogen phosphate dihydrate: 0.05 mg - Water for injection: q.s.	Number: P010029 Approval Date: December 3, 2004 Class III
INFUSE BONE GRAFT *Medtronic Sofamor Danek USA, Inc.*	INFUSE Bone Graft consists of two components: (i) a recombinant human bone morphogenetic protein solution a carrier/scaffold for the bone morphogenetic protein solution and resulting bone.	INFUSE Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP 2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). - rhBMP-2 is the active agent in INFUSE Bone Graft. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans.	Number: P000054 Approval Date: April 30, 2004 Class III

Table 5: Examples of quality risks associated with various 3D printing technologies [18].

3D Printing Technology	Parameters	Manufacturing risks	Raw material property	Quality defect in product
Selective laser Sintering (SLS)	Laser-related properties (e.g., intensity, scan speed, scan spacing)	Variability in mechanical behaviour, limited printing precision, and prolonged manufacturing time	Powder characteristics (e.g., particles size, flowability, packing density)	Variability in layers thickness
Fused deposition Modelling (FDM)	Nozzle temperature	Poor interlayer adhesion, nozzle clogging, and incomplete print formation	Filament properties (e.g., mechanical, thermal)	Filament degradation, extrusion failure, solidification complications
	Printing speed	Insufficient layer adhesion, poor printing resolution	Filament diameter	Variability in weights
Semisolid extrusion	Nozzle diameter	Low printing resolution, nozzle clogging	Semisolid material properties (e.g., extrudability, rheology, viscosity)	Inconsistency in layer thickness, inadequate printing resolution, shrinkage, collapse
	Printing pressure	Poor layer adhesion, poor printing resolution	Polymer content	Insufficient structural Integrity
Stereolithography (SLA)	Laser-related properties (e.g., intensity, scan speed, spacing)	Insufficient crosslink density, variability in layer thickness	Polymer/monomer solution properties (e.g., rheology, molecular weight, functional groups)	Poor printing resolution, Insufficient crosslinking density, poor layer adhesion
	Exposure time	Inconsistent shape, weak structural integrity	Photoiniator content	Poor printing resolution, poor layer adhesion, low crosslinking density
Digital light processing (DLP)	Laser intensity	Poor printing resolution, weak structural integrity	Polymer content	Printing failure, low structural integrity

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