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Bioprinted Constructs in the Regulatory Landscape: Current State and Future Perspectives

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Bioprinting has become one of the leading topics in biomedical research in the past decade, as demonstrated by the great surge in publications and proliferation of bioprinting facilities worldwide. Bioprinting has gained widespread popularity because of its potential to replicate complex biological structures, revolutionize in vitro testing, and tissue engineering. However, the clinical translation of bioprinted products remains a challenge. The regulatory approval of tissue-engineered products requires extensive preclinical and clinical trials with different standards worldwide. The regulatory landscape for bioprinted products is examined in the European Union, United States, China, and Australia. The current regulatory status of bioprinting is traced by exploring parallels with existing categories such as 3D printed medical devices, injectable hydrogels, and tissue engineering products. This perspective provides a comprehensive overview of the current state and regulatory landscape of bioprinted constructs, envisioning challenges, and strategies for their future integration into clinical practice.

1. Introduction

Bioprinting is used as a broad term, indicating a series of additive manufacturing techniques that process biomaterials containing cells to produce cellularized constructs for biomedical applications.[1] The materials processed via bioprinting are defined with the term "bioink" if they contain cells with or without a support hydrogel, and as "ink" or "biomaterial ink" if the cells are not included in the printing process, but seeded onto the printed constructs in a second moment.[2] Over the last decade, bioprinting has emerged as a trending topic in biomedical research. The number of publications in the field is constantly increasing as a growing number of laboratories worldwide are equipped with bioprinters. The rising research interest in bioprinting has also translated into an increased availability of bioprinters and bioinks. Bioprinting techniques are becoming widely adopted in the research fields of tissue engineering (TE) and regenerative medicine (RM), which aim to develop therapies for the treatment of diseased and damaged tissue, rather than substituting the function by transplantation or prosthetics.[3] The popularity of bioprinting in these fields is fueled by its promise to improve physiological relevance by fabricating 3D cellularized constructs with precise deposition of cells.[4] Despite significant research efforts and a growing market for bioprinters and bioinks, the number of bioprinted tissues or organ-like constructs for clinical applications remains limited. Indeed, given the multi-disciplinarity, complexity, and novelty of the field, years are required before these solutions can reach clinical applications on a large scale because of the lengthy preclinical and clinical trials necessary to receive approval. Approval of medical devices works in a set of stages worldwide with different standards in different countries, and in this perspective the European Union, the United States, China, and Australia were considered. The approval pipeline in the considered countries is summarized in **Table 1** and can be arranged in four steps[5]: 1) quality control, 2) clinical Studies, 3) premarket approval, and 4) post market surveillance.

Quality control systems ensure harmonized testing of devices and materials to guarantee the reproducibility and comparability of the results. Specific standards defined by the International Organization for Standards (ISO), the American Society for Testing and Materials (ASTM), and Good Manufacturing Practices

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Table 1. Highlights of the main aspects of the approval pathway in EU, USA, China, and in Australia.

	European Union	United States	China	Australia
	European Commission (EC), Country-Specific Notified Bodies (NB)	Food and Drug Administration (FDA)	National Medical Products Administration (NMPA)	Therapeutics Goods Administration (TGA), Australian Register of Therapeutic Goods (ARTG)
Quality Control System (Must be implemented by the manufacturer)	Harmonized standards EN ISO 13485	Good Manufacturing Practices (GMP) (21 CFR Part 820)	Harmonized standards EN ISO 13 485 plus third-party test	Premarket Assessment: A conformity assessment required to verify that the device complies with the Essential Principles (cover safety, performance and quality). Assessments by overseas regulators (FDA, EU NB, Health Canada, Singapore's Health Science Authority) are accepted if they meet Australian regulatory standards. More rigorous TGA assessment is required for high-risk devices. A positive assessment grants access to the Inclusion in the ARTG corresponds to authorization for marketing and initiates the post-marketing monitoring.
Clinical Studies	Pre-approval technical studies are always required, clinical studies depending on the risk (Classes defined by the Medical Devices Regulation MDR)	Need approval from FDA and Institutional Review Board. The nature of the studies depends on the risk associated with the device	Ethical approval is needed following the guidelines of NMPA. Multi-center trials are usually mandatory for high-risk medical devices.	
Premarket Approval	CE marking is a legal requirement for every device to be commercialized in the EU. Verified by the NB	Pre-Market Approval (PMA) submission for new devices. 510(k) Pathway for equivalents of existing devices	Premarket approval is required by NMPA based on the new rules on clinical trial inspection (2025 No.22).	
Post Market Surveillance	Reporting required from the competent authorities. European Databank on Medical Devices (EUDAMED) for information on exchange between countries	Required for high-risk devices (implants and life-sustaining). Database available to the public on FDA website	GMP qualification. Periodic safety update report (PSUR) and unique device identification (UDI) are needed for high-risk medical devices.	

(GMP) established by the Food and Drug Administration (FDA) in the United States (USA), through directives of the European Commission in the EU, and the National Medical Products Administration (NMPA) of China must be fulfilled. After appropriate technical testing, following the requirements described by the identified quality control systems (depending on the type of product and countries to be commercialized), clinical trial studies are required before obtaining pre-market approval to ensure the safety of medical devices. The extent and nature of the clinical studies depend on the level of risk associated with the device. Longer permanence in the patient's body and higher health risks associated with device failure led to assignment to higher risk categories and, consequently, longer clinical testing for approval. Once clinical studies are deemed sufficient by responsible authorities, premarket approval can be granted. In the EU, all devices need to be granted the CE mark to reach the market by the Notified Bodies (NB), which are country-specific. On the other hand, the FDA and NMPA have unified systems for their respective country. Another difference is the existence of a shorter path from the FDA, called the 510(k) pathway, which leads to quicker approval with less testing for devices that are demonstrated to be equivalent to already approved ones.[6] The 510(k) pathway was created to shorten the time required to obtain improved versions of the devices in the market. China has similar pathways for classes II and III, and innovative medical devices to accelerate the approval process. In the EU, an equivalent exists for drugs that can be proved to be biosimilars to already approved drugs, but not for medical devices. Finally, after market approval, the devices are subjected to surveillance to quickly intervene in the case of malfunctioning or health hazards.

In contrast, the medical device approval process in Australia differs significantly, with only two steps (pre-market assessment and market authorization) regulated by the Therapeutic Goods Administration (TGA).[7] The pre-market assessment includes a conformity assessment to ensure that the device complies with the essential principles of safety, performance, and quality.[8] These principles include ensuring that devices do not compromise health, are designed safely, are suitable for their intended purpose, maintain long-term safety, are not adversely affected by transport or storage, and that their benefits outweigh any risks.[9] For higher-risk devices (Class IIb and III), conformity assessment is more rigorous and may require direct evaluation by TGA.[9,10] Once pre-market requirements are met, manufacturers must apply for inclusion in the Australian Register of Therapeutic Goods (ARTG), which authorizes the device for supply in Australia and initiates post-market monitoring.

Regarding bioinks, there is still no clear indication of the steps for approval. In the preclinical study phase, currently, the only standard defining terminology and describing pre-, during, and post-printing considerations for bioinks and biomaterial inks is the designation F3559 from ASTM, published in April 2024,[1] focusing mainly on extrusion bioprinting. The wide variety of available bioprinting techniques and the equally vast array of requirements for suitable bioinks might make the writing of one univocal standard challenging. The current regulatory landscape does not include the approval of materials but only devices for specific applications, further complicating the matter. One of the great advantages of bioprinting lies in its versatility and the possibility of changing the cell density, infill, and geometry on demand, challenging the current definition of medical devices. In this perspective, the current state of bioprinted construct development is described while analyzing how they might be inserted into the regulatory landscape by taking inspiration from partially correlated categories of products already applied in clinics: 3D printed medical devices, injectable hydrogels, and TE products.

3D printed devices, similar to future bioprinted constructs, will potentially share approval challenges related to the personalization of the geometry and the consequent cascade effects on the devices (different permeability, surface area, degradation times, mechanical properties, etc.). However, common 3D printing techniques work with conventional materials (thermoplastic polymers or metals); hence, the complexity related to the use of hydrogels might be treated by making a parallel with hydrogel based medical devices.

The inclusion of biologics in a hydrogel (cells or tissue-derived materials) results in an additional layer of complexity from a regulatory perspective. By definition[1] bioprinting cannot be addressed without taking in consideration the inclusion of cells, hence in this perspective, we explored the challenges related to the inclusion of cells by comparison with the regulatory landscape of tissue-engineered products.

2. 3D Printed Devices in the Regulatory Framework

3D printing technologies allow the fabrication of objects via additive manufacturing (AM) from digital 3D models. AM has gained considerable interest in various fields thanks to the possibility of producing application-specific objects without the use of expensive molds and even achieving complex geometries that could be challenging with conventional techniques. In the biomedical field, building devices with patient-specific geometry could greatly improve the outcome of the treatments due to increased functionality and decreased discomfort for the patients. The presence of lattice or layered structures opens new possibilities for weight reduction, control of the porosity of devices, and of their surface-to-volume ratio. However, the same features carry challenges in terms of mechanical properties, fatigue life prediction, and increased degradation.[11–13]

2.1. Quality Control and Standards in Preclinical Testing

With the use of AM techniques in industry in the past decades, ISO/ASTM standards have been created to define terminology,[14] general guidelines for processing and data analysis,[15–17] requirements for industrialization,[18] and even more specific standards oriented toward the AM of polymers[19] and metals.[20,21] Not all these standards are bound to a specific field of application, but they become increasingly important in the biomedical field, particularly in the case of implanted devices, in which failure might result in fatal outcomes for the patient. Nevertheless, AM has been used in the biomedical field with countless applications ranging from patient-specific surgical phantom models to functional prosthetic implants, covering the use of various techniques and materials, from thermoplastic polymers to metals. The increase in the use of such techniques is reflected in the publication of new standards addressing AM in the medical field. In 2020, ASTM published the designation F3335 with guidelines for the removal of residues from medical devices fabricated via powder bed fusion,[22] followed by F3456 in 2022, which contains the best practices for powder re-use.[23] Typically, publications of standards follow demand from the market. It is not coincidental that the first standards for AM in the medical field focused on powder bed fusion. By searching the FDA database of devices cleared via the 510(k) pathway using "3D print" as keyword, 5 results out of 11 refer to Ti-alloy 3D printed bone fixation devices (research performed in November 2024). This result indicates that Ti-alloy bone fixation devices were among the first medical devices transitioning from traditional fabrication to AM techniques, which offer better tuning of the porosity and density, promoting biomimicry and integration with the native tissue.[24] Designing implants with patient-specific geometries often results in improved placement and patient recovery. Patient-specific geometries can be acquired directly from magnetic resonance images (MRI) or computer tomography (CT) scans of patients and converted into 3D models to use in slicing software for AM. This approach has been used in clinical applications, ranging from surgical phantom models to allow surgeons to simulate complex and risky procedures for the creation of patient-specific implants.[25–34] Following the increasing diffusion of this process, ASTM published a standard in 2022 providing the best practices for creating solid models based on patients' medical imaging, ensuring high quality and fidelity of the replicated 3D models.[35]

Standards describing best practices for production and testing are great facilitators in the preclinical study approval phase, as they save time and effort to justify their testing process via extensive literature research. As described, ISO and ASTM provide more guidelines for AM products both for general use and for biomedical applications, with the aim of gradually filling the existing gaps and covering more AM techniques used in the biomedical field.

2.2. Clinical Testing and Premarket Approval

2.2.1. EU and USA Perspectives

3D printed medical devices need, both in the EU and the USA, to follow the regulatory approval path, which divides the devices into categories based on the expected time of use, invasiveness, and hazard level for patients in case of malfunctioning. Following this division, regulatory challenges mainly arise for devices with moderate or high risks. For this perspective, only devices of Class II or higher were considered, hence those related to moderate and high health hazard risks.

Most of the 3D printed devices that have reached the market were cleared through the 510(k) premarket pathway, which requires a less extensive review process, as applicants demonstrated substantial equivalence to already approved examples. The results of a search in the public 510(k) premarket approval database,[36] using *"3D print"* as a keyword are shown in **Table 2**. These findings indicate that, at present, only a specific niche of medical devices (Ti-alloy bone fixation) has consistently progressed to clinical use, as discussed in the previous section. Limiting the approval process to equivalent existing devices hinders the true potential of AM in the biomedical field and its use in personalized medicine applications. 3D printed medical devices tailored specifically to a patient's anatomy are custom-made and hence fall under the regulations for personalized devices. In 2018, following the International Medical Device Regulators Forum, a document was published to clarify ambiguities in the definition of custom-made/personalized and adaptable devices,[37]

Table 2. Devices approved through the 510(k) pathway found by searching for "3D print" in the FDA 510(k) pre-market approval database.[54] The products are reported with the 510(k) database code, the equivalent device and extra reference devices codes and the Standards referred for testing.

Product name	510(k) code	Company	Function	Equivalent device	Equivalent Device (+ extras)	Standards for Testing
Kinos Axiom	K232595	Restor 3D	Total ankle replacement system	Kinos Axiom Total Ankle System	K192778	ASTM F2665 ISO 10993-1:2018 ASTM F2924
UNiD patient specific 3D printed TLIF cage	K190092	Medicrea International S.A.	Intervertebral body fusion system	Impix3D Print cages	K163595 (K173782)	ASTM F2077 ASTM F2267 ASTM F3001
Impix3D Print cages	K163595	Medicrea International S.A.	Intervertebral body fusion system	K2M Cascadia Interbody System	K150481	ASTM F2077 ASTM F2267
TruMatch	K173039	Materialise NV	Titanium bone plate	TruMatch CMF Titanium 3D Printed Implant System	K170272 (K133809, K063790, K080331, K083388, K042365, K053199)	ASTM F382 ISO 17665-1 ISO 14161 ISO11737-2:2009 ISO 10993–5 ISO 10993-10 ISO 10993-10 ISO 10993-11 ISO10993-18 ISO 10993-17
MiRus	K191906	MiRus LLC	Intervertebral body fusion system	MiRus Lumbar Interbody Fusion System	K182920 (K172888, K181644)	ASTM F2077-17 ASTM 2077-17 ASTM F2267-04
Segment 3D print	K180239	Additive Orthopaedics, LLC	Bone Wedge System	Bone Wedge System	K153207	NA
AA temp temporary photoreactive dental resin	K191590	Enlighten Materials Co., Ltd	Photoreactive resin for temporary dental crowns or bridges	e-dent temporary resin and extra-oral curing system	K102776	ISO 10477, ISO 10993-1, ISO 10477, ISO 868,
BB Base 3D Printing Resin for Denture Base	K191591	Enlighten Materials Co., Ltd	Photoreactive resin for temporary dental crowns or bridges	Dentca Denture Base II	K162044	ISO20795-1, ISO 10993-3, ISO10993-5, ISO10993-10, ISO10993-11

and a final document was published in 2020 to discuss the regulatory pathways of such devices.[38]

To ensure that personalized devices meet safety requirements and protect patients, healthcare professionals must provide a series of documents regarding the manufacturing process and testing of the device. This entire process was clearly described by Willemsen et al.,[26] in a two-case study of custom-made 3D-printed metal implants to treat spinal instabilities. Both cases were regarded as major spinal instabilities leading to progressive paralysis, which were untreatable by conventional approaches. The patients were treated with custom-made 3D-printed titanium implants, modeled on their CT scans and produced at a 3D-printing facility, CE-certified for the scope of modeling and production of metal medical products by AM under ISO 9001:2008, ISO 13485:2003, and EN ISO 13485:2012 certificates (3D Systems, Leuven, Belgium). The EU Medical Device Regulation regards orthopedic implants as Class III medical devices, associated with the highest risk for the patient and hence requiring extensive clinical testing and a reported timeline of 3 – 7 years.[39] Given the exceptional nature and urgency of the cases, these devices were approved under the custom-made device category described in Annex XIII of the Medical Device Regulation (MDR) with the submission of a technical note, describing the urgency of the situation, considerations on the device (design, manufacturing, testing), and a risk assessment analysis. Both surgeries were performed at Utrecht University Medical Center, in the Netherlands, which reflected on the approval pathway; the technical file submitted for a custom-made device does not need to be reviewed by the Dutch NB. The technical and regulatory details of both procedures are described in detail by the authors,[26] highlighting the time frames and efforts required for the approval of these implants. Both procedures significantly enhanced the quality of life of patients and would not have been possible without 3D printing and advanced CT technologies. For the first patient, approval of the procedure was secured within 16 weeks, and the hospital received the implant sterilized and ready for implantation at week 20. The timeline for the second procedure was significantly shorter, as the implant surgery occurred just six weeks after admission, probably due to the expertise gained by the technical and medical teams. Several similar cases have been reported worldwide, particularly for maxillofacial applications.[40,41] Some truly groundbreaking examples include the first full-eye-partial-face transplant executed in 2023 at NYU Langone Health (USA).[42] This procedure was made possible by applying 3D printing in different ways and at different stages of the operation, from careful surgical planning based on 3D CT reconstructions to the use

of custom-made surgical guides designed to align the patient and donor tissues. To date, all cases of the use of 3D-printed patient-specific implants have been guaranteed by means of exceptional or compassionate cases, and not under standard regulatory processes.

Several surgical procedures could benefit from the use of patient-specific designed prosthetics. However, 3D-printed custom-made devices will only be approved for exceptional cases until a regulatory framework is established, covering standardized procedures for devices produced with patient-specific geometries. The FDA took a stance on the matter before the European MDR by holding a public workshop in October 2014 entitled "Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing". During the workshop, opportunities and challenges of 3D printing in the medical field were discussed with stakeholders to obtain their input, which was then taken into account to publish a list of non-binding guidelines on additive manufactured products in 2017.[43] Moreover, given the existence of the 510(k) approval path for the FDA, 3D-printed devices that are not custom-made can always benefit from faster approval. This is not the case in the European legislation, which only provides approval by similarity for medicinal products recognized as biosimilars[44] (regulated under the European Medicines Agency EMA) and never for medical devices that need to be approved at a country-level by the appointed notified body and to get CE marking for approval for the market.[45]

2.2.2. China and Australia Perspectives

In 2015, China approved its first 3D printed acetabular cup product for hip replacement surgery, following a special approval pathway because of the lack of regulatory rules for customized implants.[46] The first regulation documentation on the supervision and administration of customized medical devices was launched by the NMPA in 2019,[47] which likely boosted the generation of national standards for manufacturing processes (e.g., GB/T 39252-2020[48]) and products (e.g., T/CAMDI 044–2020[49]) since 2020. By 2024, all class II and III 3D printed medical devices in China have been filed the unique device identification (UDI) to track the full lifetime of the products.[50] In 2021, the EU changed the wording of Article 123 Sec. 2 MDR. Consequently, devices that are "mass produced by means of industrial manufacturing processes" are no longer categorized as custom-made devices.[51] This definition is ambiguous, but it facilitates the use of AM to produce devices usable on an industrial scale (i.e., making metal implants by 3D printing instead of traditional techniques).

In Australia, TGA implemented a new regulatory framework in 2020[52] to ensure that personalized medical devices are subject to appropriate regulatory oversight, which was further refined by 2025.[53] This new framework introduces updated definitions, including patient-matched and adaptable medical devices, which reflect advances in medical imaging and manufacturing technologies. Prior to this change, most personalized medical devices were "custom-made" and exempt from inclusion in the ARTG. However, due to increasing complexity and risks associated with personalized devices, many now require ARTG inclusion before they can be imported into, supplied within, or exported from Australia. To support industry transition and enable the continued manufacture and supply of personalized medical devices in Australia, the TGA has established a transition period during which personalized medical devices remain exempt from ARTG inclusion until July 1, 2029. Despite this exemption, all personalized medical devices must comply with TGA regulations, particularly the Essential Principles governing safety, performance, and quality. Currently, the need for specific regulations to cover patient-specific printed devices outside of emergency or compassionate cases remains unmet.

2.3. 3D Printing at the Point-of-Care: Opportunities

Another unique feature of 3D printing is that it enables the direct production of medical devices at the point-of-care (PoC). The direct 3D printing of personalized medical devices in hospitals presents many advantages. The most common 3D printed objects following patients' MRI or CT scans at the PoC are surgical models, regarded by the FDA as Class II devices.[55] They have multiple applications in educating patients on procedures, training healthcare professionals, planning, and practicing difficult surgeries.

The in-house production of patient-specific devices has been documented to be more beneficial than outsourcing to external manufacturers. Calvo-Haro et al.,[56] analyzed the outcome of the integration of on-site 3D printing in the Department of Orthopedic Surgery and Traumatology of the Hospital General Universitario Gregorio Marañón in Madrid (Spain). They reviewed 623 procedures carried out using PoC AM from November 2015 (opening of the specialized AM unit) to March 2020 (COVID-19 pandemic onset). The authors defined the qualitative and quantitative variables related to the application, material, and printing processes. They found that the most targeted applications were *Research*, *Orthopedic Oncology*, and *Traumatology*. The authors demonstrated a predominance in the requests for surgical models (87.32%) and surgical guides (10.75%), while only a minority of the printed products were patient-specific devices for surgical intervention. This study was conducted in a research and teaching hospital licensed for in-house manufacturing of medical devices (following ISO 13485), which by nature, is an environment that facilitates translational research, equipped with specialized personnel and dedicated funding. The results showed an increased benefit from an integrated 3D printing approach throughout the treatment for specific surgical areas characterized by urgency and complexity, such as traumatology and orthopedic oncology.

Similarly, Williams et al.,[57] demonstrated the benefits of in-house 3D printing in oncological maxillofacial surgery for reconstruction of the mandible or maxilla with immediate implant and teeth. The authors presented a 12-case study in which five patients received outsourced implants and 7 received implants 3D printed in an in-house facility. The 3D printing process is well described, and the production of an implant (including printing, support removal, and cosmetic corrections) is reported to take a few hours, whereas outsourcing fabrication adds two extra weeks to the timeline. This outcome suggests the potential of 3D printing at the PoC in maxillofacial reconstructive surgery, as earlier treatment can dramatically improve the therapeutic outcome

for oncology patients.[58] The prostheses were printed using the NextDent MFH resin, which is FDA-approved for the fabrication of crowns and bridges. From a regulatory point of view, dental prosthetics are easier to assess, and dental photocurable resins are close to fully approved materials because personalized geometry has long been intrinsic to these devices. As a result, 3D printing does not introduce customization in this context but rather enhances fabrication.

2.3.1. Economic Considerations of Point-of-Care 3D Printing

Several publications have targeted the financial aspects of 3D printing at the PoC, with contrasting results. Bastawrous et al.,[59] recognized the substantial upfront investment required for equipment (printers, software, etc.) and hiring/training specialized personnel to build a PoC printing facility. Still, the authors reported that the initial cost could be offset in the long term by a reduction in the expenses from in-house production of implants compared to outsourcing. For example, Williams et al.,[57] reported that in-house printed prosthetics are considerably cheaper (≈50$) compared to outsourced ones (≈1000$), without considering the initial investment of buying the 3D printer and the license for the software involved in the STL creation process. In this regard, Ballard et al.,[60] reported cost savings from an overall decreased time in the operating room as a result of the use of patient-specific phantom models, costume-made implants, and surgical guides to speed up surgeries.

On the other hand, Ostaş et al.,[61] challenge the claim of decreased costs in their thorough narrative review of PoC Virtual Planning and 3D printing for oral and cranio-maxillofacial surgery. The authors made a significant effort to analyze aspects of 3D printing and virtual planning in surgery from a quantitative point of view over a span of seven years, in terms of planning and operating time, human resources, costs, materials, and surgical outcomes. They were faced with insufficient quantitative data and information in the literature, making in-depth cost analyses impossible. Given the absence of standardized reporting and the wide variability in costs associated with materials, printers, and software, the authors recommend revision of claims regarding cost reduction. Unsatisfactory technical reporting of the mechanical performance of 3D printed implants and the design process in the literature has also been reported by Sharma et al.[62] These studies highlight the need for multicenter analyses on the outcomes of PoC 3D printing, rather than isolated reports from single facilities, to better understand the balance between the benefits and costs of these techniques. It is worth noting that most of the mentioned studies focused on a specific sector (e.g., maxillofacial, trauma, orthopedics). Expanding the use of 3D printing laboratories for broader applications may help mitigate initial costs. Beitler et al.,[55] hypothesized that costs could also be lowered by outsourcing costly and time-consuming tests to specialized facilities (i.e., quality control of materials, mechanical testing, etc.).

2.4. 3D Printing at the Point-of-Care: Challenges

While being a good opportunity, 3D printing at the PoC blurs the lines between the fabrication facilities and the hospital, representing a gap in the current regulations for approval.[55] This results in hospitals facing increased liability as manufacturers of devices rather than users. To extend the use of this approach, a non-ambiguous definition of the role of the medical team in the case of failure of devices manufactured at the PoC is needed.

The FDA is currently working on bridging this gap to offer patients improved treatments using PoC 3D printing, while maintaining strict safety regulations and controls. In 2021, the FDA published a discussion paper on 3D printing at the PoC, following a workshop organized with stakeholders.[63] This study attempts to describe the risk associated with PoC printing by analyzing different scenarios, with different degrees of outsourcing of the printing process to external facilities. While it is not a proper regulation, the document contains some interesting points of discussion and shows the FDA's commitment to cover this matter. It is likely that in the near future, proper best practice guides will be published both by the FDA and EU notifying bodies. Meanwhile, both the FDA and scientific literature advocate for 3D printing facilities at PoC to implement strict in-house quality-control procedures.[55,59,61,63] Beitler et al.,[55] proposed a list of points that should be addressed from quality systems for best practices to consider in PoC 3D printing.

Some of them are obvious, such as material selection and biocompatibility, the standardization of the infill and deposition process to guarantee reproducibility, and prevent asymmetries in the device geometry and performance. Some of them are less trivial, for example, they advocate for a labeling and expiration date of the patient-specific 3D printed device, impressed on the device itself or incorporated during printing. The label will ensure that the device will be assigned to the correct patient, at the same time the expiration date might be correlated to the date in which the MRI or CT scan was taken to build the STL model, as patient's anatomy might change (especially in case of some degenerative diseases or for pediatric patients). Sterilization of 3D printed devices should also be addressed by regulatory bodies to ensure the prevention of infections and the sterilization process to impact the mechanical properties and functionality of the devices.

3. Hydrogels in the Regulatory Framework

Hydrogels are biphasic systems composed of a polymeric network and an aqueous phase. They can originate from natural (polysaccharides and proteins) or synthetic polymers (e.g., PEG), which can form networks characterized by stable chemical bonds or physical interactions (e.g., entanglements and electrostatic interactions). Hydrogels have been popular materials in the biomedical field for decades for countless applications, due to their tunable properties, possibility of drug loading, and similarity to the extracellular matrix. Many medical products used in clinical applications are based on hydrogels (e.g., drug delivery systems, cell delivery systems, contact lenses, and anti-adherent membranes[64]). Nevertheless, the regulations on novel biofabrication techniques, such as bioprinting, are still to be fully developed. Injectable hydrogels must meet specific requirements for ease of injection through a nozzle, to maintain a defined volume, shape, and sustain mechanical load in situ. The versatility of these materials provides a multitude of possibilities for tuning their rheology and gelation speed, which have been extensively described in the literature.[65,66] Most of the design criteria to

Table 3. Standards covering biomaterials and hydrogels use in the biomedical field.

Material	Standard	Title
Chitosan	F2103	Standard Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
Alginate	F2150	Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Regenerative Medicine and Tissue-Engineered Medical Products
	F2315	Standard Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
Collagen	F3089	Standard Guide for Characterization and Standardization of Polymerizable Collagen-Based Products and Associated Collagen-Cell Interactions
	F2212	Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue-Engineered Medical Products (TEMPs)

follow in the engineering of injectable hydrogels are common to bioinks meant for extrusion-based bioprinting; hence, we review the possible steps of regulatory approval of bioinks by comparing them to injectable hydrogels.

3.1. Hydrogels in Quality Control Standards and in the Market

The ISO/ASTM standards are available for the extraction, testing, and use of the most common hydrogels for biomedical applications. For example, for biopolymers extracted from marine sources, designation F2103 refers to the characterization and testing of chitosan from marine sources for biomedical and pharmaceutical applications,[67] designation F2150 refers to the characterization and testing of biomaterials for use in biomedical and TE Medical Products,[68] and designation F2315 refers to the encapsulation of living cells or tissues in alginate.[69] Moreover, there are some standards for the characterization of collagens for biomedical applications, such as designations F3089 and F2212.[70,71]

The existing standards listed in **Table 3** are still insufficient to cover the large spectrum of hydrogels used in research. To accommodate biofabrication and biocompatibility requirements, researchers have explored a variety of hydrogels of both natural and synthetic origin, with and without chemical modifications to tune their properties.

The most common modifications to the polymeric backbone are aimed at providing the possibility of covalent crosslinking or introducing biological cues. The most diffused chemical modification for covalent crosslinking is methacrylation, which allows for the formation of hydrogels via free radical photopolymerization in the presence of a photo-initiator and light irradiation. Methacrylated polymers, both synthetic (e.g., PEGMA) and natural (e.g., GelMA, AlgMA, ColMA), have become widely used in research, and some of these polymers are now sold as reagents. GelMA, AlgMA, HAMA, ColMA, and SilMA can now be purchased from several distributors, with varying degrees of substitution and molecular weights. Some manufacturers are now also selling methacrylated polymers with GMP certification for pharmaceutical applications (e.g., X-Pure GelMA from Rousselot, GelMA-INX© from BioInx, HAMA, ColMA from Matexcel, and HAMA from Bláfar).

Other modifications are available to include also different crosslinking triggers than photo-, such as phenol or catechol modified polymers for enzymatic crosslinking, or polymers modified with functional groups to enable click-chemistry. A few of these modified polymers are available for purchase, albeit less commonly than methacrylated ones. For example, Rousselot commercializes research-grade gelatin with pendant phenol groups (X-Pure GelDAT), or PEG is available with various pending groups and functionalities for click chemistry (i.e., azide and alkyne). In addition to covalent crosslinking, modifications with novel properties are appearing in the market. For example, BioInX recently introduced a GMP grade polyester resin for DLP with both photocrosslinking and shape memory properties (Degres-INX©). The library of hydrogels used and modifications researched is continuously evolving and expanding. Consequently, maintaining new standards and good practices is a challenge.

ASTM published designation F2027,[68] which is the *Standard Guide for Characterization and Testing of Raw or Starting Materials for Tissue-Engineered Medical Products*. This guideline represents an attempt to provide a more universal set of testing procedures for raw materials than focusing on a single material at a time, covering all material classes (ceramics, metals, polymers, and composites), referencing a long list of existing standards on characterization practices for such materials to be used in TE applications. Providing more universal guidelines on how to handle raw materials is a way to consider the use of novel materials and chemical modifications, overcoming some limitations of the existing standards. For instance, the aforementioned standards on alginate do not cover any form of modification and crosslinking that is not ionic and are, therefore, outdated compared to research.

3.2. Hydrogels as Inks: Filling the Regulatory Gap

While generalization helps expand the materials covered by standards, it also means that the guidelines will be less specific. The requirements for the materials in designation F2027[68] are broadly listed, and hydrogels are not addressed as a self-standing category but are included in the polymer classification, referring to the standards for chitosan, alginate, and collagen mentioned earlier. The physical and mechanical requirements listed for polymers are: "*structure—primary/secondary, powder size distribution, water absorption or swelling %, glass transition temperature, melting point, crystallinity, density (true, bulk, or apparent), elastic modulus, ultimate tensile strength, compressive strength*". There is no

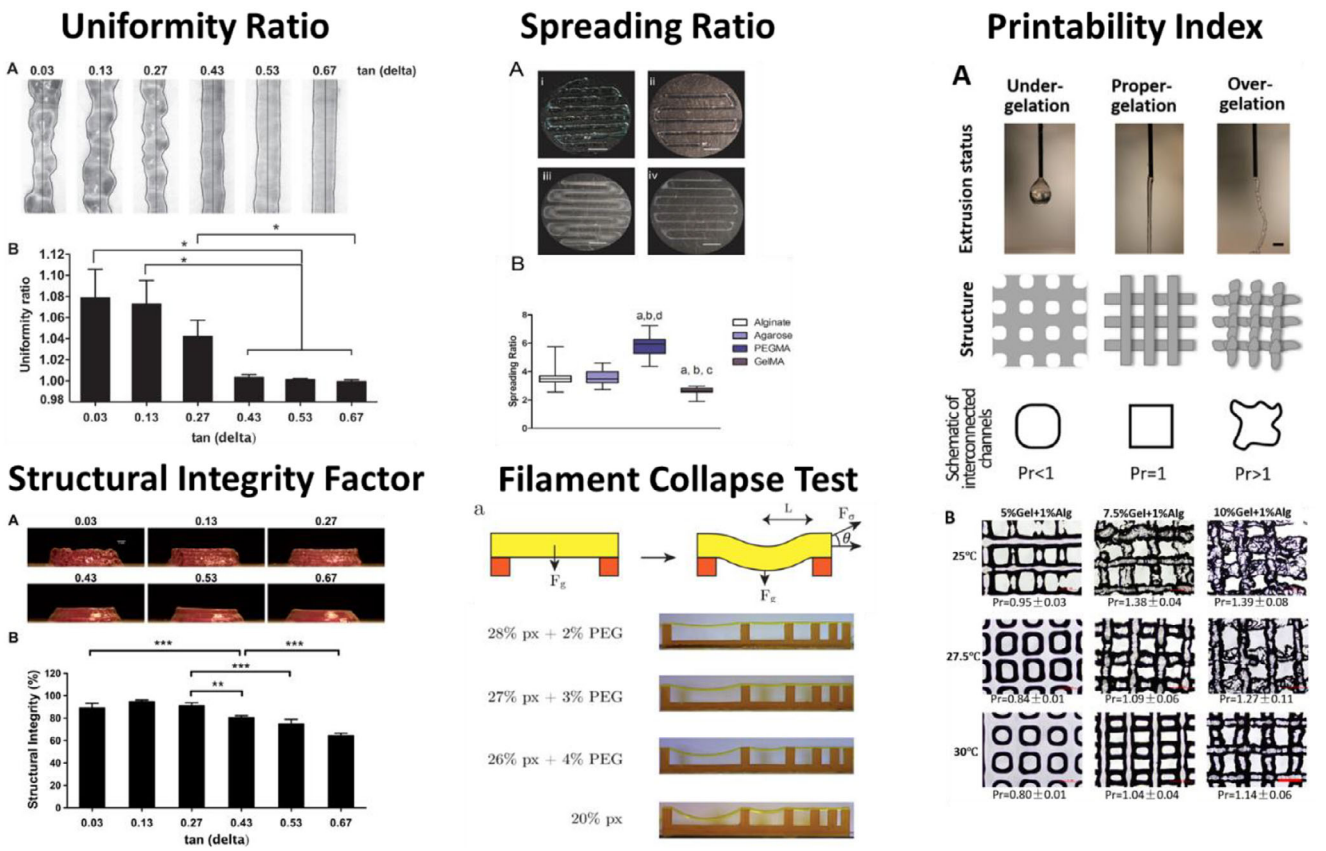

Figure 1. Examples of common indexes to determine printability of widespread use in literature regarding extrusion bioprinting. Figures adapted with permission from[80] Uniformity ratio and Structural Integrity,[81] Filament Collapse Test,[82] Spreading Ratio, and[83] Printability Index.

information on the required rheological properties of the prepolymer solution or the viscoelastic properties of hydrogels, despite these being fundamental features that strongly affect hydrogel applications. The rheology of hydrogel prepolymer solutions is a determinant parameter for testing any application involving extrusion or injection, such as extrusion-based and inkjet bioprinting. These techniques have different rheological requirements, and in both categories, ink properties determine the possibility of deposition, cell viability, and geometrical accuracy. Extensive research has been conducted on the effect of rheology on printing accuracy, which translated into many publications reporting models to predict printability from ink properties and general best practices and methods to assess printability.[72–77] The recently published designation F3659 on bioinks focuses on extrusion bioprinting and mentions the use of rheology to assess crosslinking; however, it fails to provide in-depth information about the methods to follow and data analysis. There are several standards on rheology for different applications (e.g., cement rheology, asphalt rheology, resin and silicone rheology, etc.) that can provide useful insight into the techniques and viscoelastic property characterization through rheology; however, they fail to account for hydrogel-specific features (e.g., maintaining hydration during testing).

Despite the lack of specific standards for determining the rheology of hydrogels for bioprinting, the literature is converging toward some testing methods. Some examples of indexes that are popular in the literature for determining printability are shown in **Figure 1**. The Uniformity ratio and spreading ratio are common preliminary tests used to assess the quality of extruded filaments. The printability index is the most widely used method to determine the geometrical accuracy of constructs quickly and inexpensively. Hydrogels are viscoelastic and generally softer than thermoplastic polymers used for standard 3D printing; hence, it is also common to test whether inks are self-standing, which is made by printing on distanced pillars to evaluate filament collapse, or by checking the structural integrity when printing several layers. With these developments, a harmonized standard guideline on the determination of the rheological properties of inks and on the printability assessment of inks is expected. Oscillatory rheological measurements are often performed to determine the viscoelastic properties of hydrogels after crosslinking. Measuring the viscoelastic properties via rheology offers advantages because of the high sensitivity of the technique and for practical reasons (the same sample can be used for characterization of the prepolymer solution and the hydrogel if crosslinking in situ on the rheometer is possible). Dynamic mechanical testing is necessary to measure both viscous and elastic contributions to the modulus. There is growing interest in how tuning the viscoelasticity and relaxation times of hydrogels results in a different biological response of cells cultured on top or encapsulated in the materials. The literature shows how gels with the same storage modulus, but varying loss moduli result in different

cell responses.[78,79] This emphasizes the need for standards to provide harmonized procedures, ensuring the possibility of comparing data, and facilitating the advancement of research.

3.3. Injectable Hydrogels in the Clinic

In the EU, injectable hydrogels are regarded as Class II or Class III medical devices (under Commission Regulation (EU) 2017/745 on Active Implantable Medical Devices (AIMD) 2017/745[84,85]). Similarly, in Australia, injectable hydrogels are classified as Class IIb or Class III medical devices depending on both surgical invasiveness and biological activity. Interestingly, if the intended application of injectable hydrogels is for tissue augmentation or cosmetic use, such product should comply with the Poisons Standard of TGA.[86] In China, injectable hydrogels are usually regarded as class III medical devices according to safety standards (ISO 10993) and NMPA guidelines.[87] Class III is associated with the highest risk, hence requiring the longest and most extensive preclinical and clinical testing before approval for the market.

Hydrogels can be either from natural origin or synthetic. Synthetic hydrogels are easier to synthesize with well-defined properties (e.g., controlled composition, molecular weight) compared to natural-based hydrogels, but they often perform worse in terms of biological response. Polymers of natural origin are growing in both research interest and presence in the clinic, owing to their outstanding biological response, regardless of the challenges that they present in terms of batch-to-batch variability and poor mechanical properties.

Natural hydrogels can be extracted from animal sources (e.g., hyaluronic acid, chitosan, collagen, etc.), from plants or bacteria (e.g., alginate, cellulose), or from biological samples (e.g., blood, decellularized ECM, etc.). Each source has several benefits and challenges. For instance, food waste byproducts are a cheap and widely available source for the extraction of animal-origin hydrogels, but they present risks of possible transfer of diseases, such as bovine spongiform encephalopathy (BSE).[84] Marine sources are less risky in terms of disease transmission, but extraction procedures still require optimization, and plant-based sources usually result in hydrogels with lower bioactivity.

Currently, most animal-derived hydrogel formulations present in the clinic are injectable collagen or hyaluronic hydrogel formulations for osteoarthritis or aesthetic surgery applications.[85,88] An overview of injectable hydrogels present in the clinic or undergoing clinical studies was provided by Mandal et al.,[88] The authors divided the hydrogels into categories based on their structure (patches, injectables, fillers, bulk gels) and chemistry (natural or synthetic origin), focusing on products already in the clinic, or on their way to approval (undergoing stage II and III clinical studies). They reported 28 clinically approved injectable hydrogel formulations, mostly synthetic and natural dermal fillers, with varying crosslinking mechanisms. The oldest approved dermal fillers reported are Zyplast(R) and Zyderm(R) (Inamed Corporation/Allergan, Inc.), both based on bovine collagen and approved by the FDA and EMA in 1981.[88] Hyaluronic acid injections have become a staple as dermal fillers and as a palliative treatment for osteoarthritis (intra-articular periodic injections). Alonso et al.,[85] reviewed the challenges of industrialization and commercialization of natural-based injectable hydrogels using hyaluronic acid as a practical example. Mandal et al.,[88] described different injectable hydrogels, in addition to hyaluronic acid filling, clinically approved for various applications in which they act as a physical barrier. For example, in cancer therapy, hyaluronic acid is used to preserve healthy tissue from excessive radiation exposure, to prevent urinary incontinence or even heart failure. In 2014, EMA approved an alginate-based formulation for the treatment of heart failure in patients with an enlarged left ventricle (Algisyl-LVR Hydrogel Implant from LoneStar Heart, Inc.). This product consists of an injection of alginate into the heart muscle, ionically crosslinked in situ, forming a non-resorbable barrier that recovers a more consistent and steady blood flow, preventing the advancement of heart failure. Variations in this approved formulation are currently under clinical trial together with many other injectable hydrogels. The most common areas of application of the reported clinical trials are osteoarthritis treatment, cancer treatment (imaging, spacing for radiation therapy, biopsy), and tissue regeneration (kidney, myocardium, uterus).[88]

3.3.1. Translational and Regulatory Challenges for Injectable Hydrogels

From the cited examples, it is clear that while the use of chemically modified hydrogels is common at the research level, this is not the case in clinical applications. Avoiding chemical modification and using formulation based on hydrogels that are already GMP approved by the Pharmacopoeia (e.g., gelatin) speeds up the regulatory process, although limiting possibilities. For instance, Mandal et al.,[88] reported three gelatin-based hydrogels in a clinical trial for tissue regeneration (in the kidney and myocardium). Unmodified gelatin might work as an injectable hydrogel to promote tissue regeneration in restricted areas, but it degrades easily and is not suitable as a bioink because of its low geometrical accuracy.

All hydrogels intended for injection or implants need to cause minimal immune response, both to avoid inflammation and possible fibrosis, and to prevent material modification following the local physiochemical changes triggered by the immune response. Mandal et al.,[88] identified some key obstacles in the clinical translation of injectable hydrogels, all of which are limiting factors shared by bioinks. Hurdles with hydrogels, particularly natural-based hydrogels, begin at the synthesis step. The vast selection of hydrogels investigated at the research level is often synthesized in small batches for preclinical assessments and faces major scale-up and standardization issues. Polymers of natural origin face technical industrialization challenges due to batch-to-batch variations in terms of molecular weight and composition, related to the source of extraction. Issues in guaranteeing reproducibility among batches are also reflected in issues along the regulatory pathway, as it may be difficult to set up a quality management system and control parameters when the molecular weight and composition of the polymers fluctuate.[85] In addition, implementing good manufacturing practices in line with regulatory requirements for pharmaceutical and biomedical applications is challenging as most natural hydrogels undergo degradation when subjected to sterilization processes. Regulatory-wise, the fact that hydrogels and crosslinking methods are diverse

which makes it difficult to frame and precisely classify them when compared to drugs. Moreover, the FDA, NMPA, and EU regard injectable hydrogels as medical devices and not as drugs, making clinical testing and approval long. The FDA often does not guarantee approval of hydrogel-based products via 510(k) Pre-Market Notification but it requires additional tests.[88]

3.4. Injectable Hydrogels as Combination Products

The approval pathway is further complicated when hydrogels are used as drug or cell carriers. Clinically approved injectable hydrogels for various applications include lidocaine, which reduces pain and discomfort after injection.[89] Other applications of hydrogels as injectable drug carriers include spinal fusion and cancer therapies. Using injectable hydrogels as carriers for cells and/or therapeutics implies engineering of the deposition method to prevent damage to the carried drugs/cells, as well as tuning of the material to guarantee an appropriate cell response and tuned drug release.

The presence of a drug or drug-secreting cells in a hydrogel makes the medical device a combination product. Combination products, both for EMA and FDA, are medicinal products incorporating medical devices.[90,91] This category includes a vast array of medical devices, ranging from pre-filled syringes to drug-releasing medical implants. From a practical point of view, belonging to two different categories implies longer approval pathways. Combinatory products require approval for both the medicinal product and the medical device, separately and in combination. The manufacturer must verify the possible effects of the device on the safety and efficacy of the drug. Similarly, additional documentation may be requested by notifying bodies to assess whether the presence of the drug affects the device in any way.

To put this more into perspective, some practical examples of the synergistic effects of commonly used hydrogels and drugs are provided hereafter. As previously described, the local anesthetic lidocaine is a commonly used additive in dermal fillers. Besides providing pain relief, lidocaine has been demonstrated to be a powerful radical scavenger, similar to several other anesthetics.[92,93] Frequently applied crosslinking methods rely on the presence of radicals. For instance, photocrosslinking of hydrogels (e.g., GelMA) is triggered by light irradiation and the use of free radical photoinitiators, such as LAP, Irgacure 907, Ruthenium, Riboflavin.[94] Another example is the enzymatic dityrosine crosslinking triggered by hydroxyl radicals in the presence of horseradish peroxidase. For all these crosslinking initiators, the presence of a drug acting as a radical scavenger in the hydrogel precursor solution might affect both the kinetics and crosslinking degree, justifying a re-assessment of the medical device (the hydrogel) due to combination with a medicinal product (the anesthetic drug). Conversely, there may be cases in which the medical device may affect the medicinal product. For example, if a specific growth factor is considered in such photo-crosslinkable hydrogel formulations, the radicals released during irradiation might damage the growth factor.[95]

Consequently, obtaining market approval for these combination products requires additional tests and time even if a previously approved medical device and an approved medicinal product are combined, the process can take up to 10 years.[88] In Section 9 of the *Guideline on the quality requirements for drug-device combinations*,[90] EMA recognizes the difficulties for regulatory agencies to keep up with the constant flow of emerging technologies and solutions, and suggests manufacturers to seek advice through competent authorities early on and when seeking to obtain market authorization for particularly novel polymers.

An additional challenge emerges when the injection instrument is specific to the hydrogel formulation and not a common consumable or surgical tool. In this specific case, the injection tool is part of the combination product and must be tested for safety. Mladenovska et al. speculated that in the case of bioprinting, the printing hardware might similarly take part in the combination product.[8] This topic must be addressed by specific regulations.

4. Tissue-Engineered Products

In the 20th century, medicine underwent a paradigm shift from an approach primarily focused on symptom management to the RM concept.[96,97] RM aims to restore the functionality of organs and tissues, rather than substituting them with transplantation or prosthetics. This shift was made possible by technological advances in both the medical and materials engineering fields. In 1993, Langer and Vacanti coined the term TE[98] to indicate an emerging field that combined biomaterial scaffolds and cells to sustain the body in regenerating native tissue function. Since its inception, the field has evolved and now includes various sophisticated approaches, such as stem cell-based therapies and gene therapy.

Atala et al. were pioneers in the field and implanted engineered bladder tissues, made of autologous cells cultured in a biodegradable scaffold in 1999.[99] Despite the good results, the surgeries were performed for compassionate cases and not on a representative pre-defined group; hence, it could not be considered a clinical trial. At that time, no regulatory pathway was in place to account for such innovative and complex products.

Currently, several tissue-engineered and RM products have been approved for clinical use worldwide.[100–103] Owing to the novelty and complexity of these therapies, new regulatory pathways have been identified. The EC introduced the term *Advanced Therapy Medicinal Products* (ATMPs) for the first time in 2003, to indicate a variety of innovative medicinal products ranging from gene therapies to tissue-engineered products (added in the update of 2009).[104] To overcome the lack of expertise in such novel and complex fields, the EU delegated a review of premarket approval for ATMPs to an independent committee, the Committee for Advanced Therapies (CAT), who submitted an opinion paper on the requests to the EC responsible for the final approval. Similarly, the FDA created the *Regenerative Medicine Advanced Therapy* (RMAT) designation in 2016.

In regulatory definitions, both in the EU and FDA framework, bioinks would fall into the category of "Combination products", since they combine the use of biologics (somatic cells, engineered cells, growth factors, etc.) with a medical device (hydrogels and their delivery system are categorized as medical devices). The EU accepts both the definition of "Combined ATMPs" when the biologics prevail on the function of the product, and "Combination products" when the device part is prevalent on the function. In this perspective, bioinks and bioprinted constructs were

addressed as "medical devices" or "combination products" to use a universal notation, since not all regulatory authorities officially use the term "ATMPs".

In Australia, tissue-engineered products are regulated under the biologicals framework and are typically classified as Class 3 or Class 4 biologicals, depending on the degree of cell or tissue manipulation and associated risk. If the product incorporates a medical device component—such as a biomaterial scaffold—it may be regulated as a combined Advanced Therapy Medicinal Product (ATMP). This dual classification adds regulatory complexity, requiring the product to meet both the biological and medical device standards.[105] The regulatory pathway involves compliance with the Australian Regulatory Guidelines for Biologicals (ARGB), conducting appropriate clinical trials, and obtaining inclusion in the ARTG before the product can be legally supplied.

4.1. Cell-Based Products

The regulatory aspects of cell-based therapy depend on the source, level of cell manipulation, and method of administration.[106,107] Implanted cells can be autologous, and hence harvested from the patients themselves, or they can be allografts, and hence come from a donor. Autologous cells prevent the risk of rejection; however, they are not always a viable option as they may be scarce or unavailable in diseased patients. Moreover, they might be challenging to harvest and cause morbidity at the extraction site. Donor cells are optimal for overcoming issues with harvesting cells directly from patients; however, caution is required to prevent rejection and disease transmission. Stem cells have assumed a pivotal role in RM, both in the form of autografts and allografts.[108,109] Stem cells are popular because of their ability to differentiate into several cell lineages. Embryonic stem cells preserve their highest potency, but their use poses ethical questions; hence, stem cell therapies rely on different sources.

Human mesenchymal stem/stromal cells (hMSCs) are of particular interest in cell therapy and TE research because they are very good candidates for both autologous implants and donations, as they can be harvested with minimally invasive procedures from bone marrow, adipose tissue, dental pulp, or donated birth tissues such as the placenta or umbilical cord.[110] Moreover, hMSCs are relatively easy to isolate and expand while preserving differentiation capabilities, for example toward bone[111] or cardiomyocytes[112] and are currently approved for diverse applications, such as treatment of autoimmune disease, bone defects, fistulas, osteoarthritis, and under trial for many more future applications.[113] Potency can be induced in somatic cells to create induced pluripotent stem cells (iPSCs). iPSCs are in the spotlight of stem cells research for in vitro modeling and RM, and are currently in use in clinical trials to treat various diseases (e.g., Parkinson's disease, spinal cord injuries, etc.[114]) because of the possibility of generating both progenitors and somatic cells. Kim et al.,[115] highlighted some companies working on iPSC-based therapies worldwide. Despite their potential, iPSCs clinical use is still hindered due to higher risks associated with off-target differentiation and teratoma formation.[116,117]

Cell therapies are regulated as advanced therapy medicinal products (ATMPs) in the EU, whereas the FDA regulates them as cellular and gene therapies (CGTs). In China, cell products that rely on the cell-derived biological cues are regulated as drugs instead of as medical devices.[87] When cell therapy is administered in combination with a biomaterial or scaffold, it is regarded as a combination product, with the medical device being classified as Class III. The first ATMP that reached the market was approved in 2009, followed by several others, accounting for 24 ATMPs in 2023.[118] In Australia, Ortho-ACI, developed by Orthocell Limited[119] was the first tissue-engineered product listed on the ARTG. It involves the implantation of a patient's own cartilage cells (autologous chondrocytes),[120] and because of the use of human cells and significant manipulation during processing, it is regulated under the biologicals framework.[121] Prior to full approval, Orthocell operated under a TGA-issued manufacturing license, but ARTG inclusion enabled commercial distribution and reimbursement processes both in Australia and internationally, including in Hong Kong, Singapore, and New Zealand.

Cells often need to be cultured and expanded to appropriate concentrations to guarantee clinical use. This is the case regardless of the cell nature, and accounts for primary, stem, and modified cell lines.[122] The more cells are manipulated before implantation, the higher is the risk of contamination and undesired differentiation. Recommendations on how to handle and test pre-implantation and expansion are in place both from the FDA[122] and the EU[123] to mitigate risks and safeguard patients. Another way governmental bodies offer both control and assistance in mitigating the risks associated with cell therapies is via GMP certifications. Cell-based products must be extracted and handled following GMP in Europe, China, Australia and in the United States. The assignment of GMP certification follows similar rules internationally, and for such novel products, it is usually based on a case-to-case evaluation of the production site and process.[124] The fact that GMP certification is highly product-specific allows the consideration of a wide variety of production/extraction sites, including academic and hospital settings, which are often relevant during the first stages of development of novel and advanced therapies.[125] However, this also results in a lack of harmonization between international organizations, that might perform GMP evaluations at different developmental stages and with different requirements.[124]

4.2. Tissue-Derived Biomaterials

Encapsulation of cells in a biomaterial might aid in vivo cell delivery by providing protection from shear stress during injection, control of the delivery location, or isolation from the host, if needed for a specific application (e.g., allogenic transplant). Moreover, the carrier biomaterial can act as a tool to direct cell behavior via mechano-transduction or through chemical signaling, depending on its composition (e.g., with RGD motifs triggering cell adhesion).[114]

Tissue-derived biomaterials are derived from human or animal tissues. The decellularized extracellular matrix (dECM) provides an ideal culture environment for cells, thanks to the preservation of tissue-specific biochemical cues.[126] The use of animal-derived dECM in the form of xenografts is common because of the high availability of this source. Many products based on animal dECM are available for research purposes[126,127] and

Table 4. Overview of matrix-based biomaterials of human, synthetic, and animal origin.

Human tissue origin products			
Product name	Description	Origin	Company
ObaGel	3D scaffold for cell culture	blood	Obatala
ObaGel ECM	Tunable stiffness hydrogel	adipose tissue/blood	
HumaDerm	Collagen (type I, type IV, or type V), lyophilized, in solution, or as coated plates	skin	Humabiologics
HumaDerMA	Collagen type I methacrylate, lyophilized	skin	
Huma OsteoGelatin	Gelatin, high or medium bloom, lyophilized	bones	
Huma OsteoGelMA	Methacrylated version of Huma OsteoGelatin		
HumaMatrix	Lyophilized universal dECM	birth tissues	
Huma OsteoMatrix	dECM plate coating solution	bones	
Huma CartiMatrix		cartilage	
Huma TenoMatrix		tendons	
Huma MyoMatrix		Muscoskeletal tissues	
Huma DermiMatrix		skin	
Huma AdipoMatrix		adipose	
Huma HepatoMatrix		liver	
Huma PneumoMatrix		lung	
Huma CardioMatrix		heart	
Huma NephroMatrix		kidney	
Huma PancreoMatrix		pancreas	
DayZero Membrane Patch	Sheets of dehydrated ready to use dECM (scaffold)	Amniotic membrane	ZeoScientifix
Xeno-free Matrix Products			
Product name	*Description*	*Origin*	*Company*
VitroGel kits	Xeno-free hydrogels mimicking ECM	Synthetic	TheWellBioScience
GrowDex Hydrogel			UPM biomedicals
Xeno-derived Matrix Products			
Product name	*Description*	*Origin*	*Company*
Matrigel	Solubilized basement membrane extract	Engelbreth-Holm-Swarm mouse sarcoma	Corning
Cultrex UltiMatrix	Solubilized basement membrane extract		Trevigen
Geltrex	Solubilized basement membrane extract		Gibco

clinical applications, such as wound healing, cardiovascular surgery, and bone regeneration.[128,129] The use of animal-derived materials has some drawbacks and risks related to the possibility of pathogen transmission and immunogenic reactions. Kasravi et al.,[130] reviewed the current state-of-the-art use of dECM materials and strategies to mitigate the risk of immunogenic reactions. In the late 90s the topic of disease transmission from animal-derived medical products became tragically popular due to the spread of spongiform encephalopathy. The spongiform encephalopathy epidemic sparked discussions on the handling and testing of animal-based materials, resulting in discussion documents and recommendations from responsible government organizations, regularly updated in the last decades.[131,132]

The use of human-derived hydrogels has been explored to lower risks of pathogen transmission compared to animal-derived sources and to verify improved biocompatibility. The commercially available matrix materials of human, animal, and synthetic origin are summarized in **Table 4**. Currently, some companies provide human-derived scaffolds and hydrogels for research purposes. Obatala produced ObaGel, the first commercialized human-derived scaffold made of adipose tissue-derived decellularized matrix. Currently, the company is commercializing human adipose tissue and blood-derived dECM both in the form of hydrogel and coating for plates, to substitute the use of tumor-derived murine matrices, which are still extensively used in research (e.g., Matrigel, Cultrex, etc.), but are not approved for clinical use.[133,134] Humabiologics is another company commercializing human-derived hydrogels for RM. Humabiologics is both ISO 13485:2016 certified and GMP compliant, and offer an array of organ specific coating proteins and hydrogel precursors for cell culture, including human-derived GelMa (HumaOsteoGelMA) and ColMA (HumaDerMA). Altunbek et al.,[135] modified human-derived gelatin from Humabiologics (OsteoGelatin) to produce human derived GelMA (hGelMA). hGelMA was synthesized with varying degrees of methacrylation to produce tunable hydrogels with a resulting compressive modulus ranging from a few kPa to ≈25 kPa, to culture human dermal fibroblasts (hDF) and hMSCs, proving the possibility of tuning the hydrogels

properties and successful culture on top and encapsulation of the two cell types. While human-derived matrices might bring advantages, the differences between the different sources are unclear, and it might not justify the replacement of GelMA produced from animals due to the potential limitations in terms of sourcing of human material, as described above.

An interesting comparison between Matrigel and endometrium-derived dECM from animals and humans was performed by Jamaluddin et al.,[136] Both human and murine endometrial organoids were cultured in these matrices, and the results showed that both endometrial dECM sources were better than Matrigel in providing appropriate signaling and in producing organoids that were more similar to native tissue. Furthermore, some differences were observed in human- and bovine-derived dECM-grown organoids, although the performance of the animal hydrogels was satisfactory, and the authors argued that animal-derived tissue-specific dECM could be easier to translate to clinics while providing more relevant results than tumor-derived matrices. Another example of a comparison between human-derived hydrogels and Matrigel is the work of Belgodere et al.,[133] who developed an extraction protocol of decellularized hydrogels from human birth tissue samples and named the obtained product XGel. The authors performed deep proteomic characterization of the gel and compared it with the commercial human-based matrix gel (ObaGel, Obatala) and Matrigel. The results showed that the combination of XGel and ObaGel outperformed Matrigel in terms of completeness of the proteomics profile, tunability of the mechanical properties and biocompatibility, as assessed by culturing and differentiating human cells on top and encapsulated within. Additional examples of matrices isolated from different tissue sources have been also reported in literature. Ramzan et al.,[137] developed umbilical tissue-derived hydrogels for the proliferation and chondrogenic differentiation of MSCs, and Pu et al.,[138] used decellularized human adipose tissue to produce injectable hydrogels for culturing adipose-derived stem cells. Despite the promising cell culture results of these studies, they still fail to demonstrate the superiority of using human-derived hydrogels, as they do not provide a comparison with other sources (e.g., Matrigel or animal-derived dECM). Hoffman et al.,[139] demonstrated that the use of human-derived lung dECM provided better outcomes than Matrigel as a substrate to culture iPSCs and differentiate them into alveolar type 2 cells (ATP2s). In this study, the cell morphology and gene expression were improved while facilitating induced alveolar type 2 epithelial cell (iAT2) alveolosphere formation, showing the potential of human derived dECM, albeit not providing an animal-derived dECM control.

4.3. Cell-Derived Biomaterials

An alternative source of human dECM is the matrix secreted by human stem cells.[140] The literature on the extraction and engineering of ECM from cell-stem culture is growing, as this circumvents the need for donated tissues or organs. Sart et al.,[141] reviewed different protocols, sources, characterization, and performance of cell-derived dECM (c-dECM). Stem cells sourcing can be performed using non-invasive procedures or from body fluids. Xiong et al.,[142] evaluated the use of c-dECM derived from the culture of human urine-derived stem cells (hUDSCs) as a substrate for cell culture. They found that the ECM derived from hUDSCs was rich in fibronectin and verified its suitability for used in ligament regeneration. They tested the in vitro culture of human periodontal ligament cells (hPDLSCs) and found that their c-dECM sustains hPDLSCs adhesion and proliferation, and promotes both angio- and osteo-differentiation. Osteogenic and angiogenic differentiation of MSCs using c-dECM obtained from different cell cultures has shown by several groups.[143–145] Kornsuthisopon et al.,[143] demonstrated increased mineralization when gingival MSCs were cultured in a scaffold made of c-dECM produced from human dental pulp cells. Both the dental pulp and gingival tissues were harvested during the normal planned treatment of patients, representing a non-invasive source of cells and biomaterials for treatment. Stem cells-based therapies have already reached the clinical stage; hence, both regulatory and practical aspects are in place for the isolation, culture, and expansion. The use of human-derived ECM obtained from decellularized cell culture could be pivotal in solving organ shortages and in overcoming the use of animal products. This field, however, is incredibly novel, and while regulatory measures are already in place for cell-based therapies, for c-dECM to reach the clinic, further optimization is required to establish protocols, scale-up production, and ensure sufficient reproducibility and mechanical properties of the obtained hydrogels. Recently, the production of synthetic matrix-based materials has also emerged as an alternative source, by mixing proteins from plant-based and bacterial sources, to mimic the dECM. These products are only available as coatings for research purposes; however, they aim to overcome the reproducibility and ethical issues associated with tissue and cell-derived materials.

4.4. Tissue-Based Products in the Clinical and Regulatory Landscape

Tissue-based products contain cells (genetically modified or not) and/or tissue. A combination of tissue-based products and non-human origin hydrogels belongs to the category of combination ATMPs in Europe, and generally, combination products bring together biologics and a device (the hydrogel and/or the delivery system) in a single therapy. Considering this definition, both bioinks and inks containing dECM are tissue-based products.

The use of human-sourced biological material to make a bioink uncovers some practical considerations in addition to regulatory ones. Tissue samples can be obtained directly from patients for autologous implants or donors. Autologous extraction prevents the possibility of rejection, but it may imply morbidity from the site of extraction. Besides morbidity, autologous tissue extraction might not always be a suitable solution due to a lack of healthy tissue to extract or due to lengthy processing steps to convert a tissue sample into an implantable hydrogel or implantable cells, which might not comply with the therapeutic needs of the patient. Biological material may also be sourced from a donor, termed allograft material, when compatibility is ensured (e.g., bone marrow and blood). Allograft materials can either be extracted from donors or sourced from biobanks. All of these scenarios imply

the procedures to be carried out in certified facilities by trained (medical) personnel, ethical approval, and other considerations.

As previously described for 3D-printed implants, performing manufacturing at the point of care or outsourcing it to an external manufacturer is currently a viable choice. Conversely, in the case of bioprinting of tissue-based products, both options face additional challenges. While off-site production of cellularized medical devices introduces challenges for transport of the constructs before implantation, forcing to find solutions to avoid damage or cell death during shipping (i.e., transport with physiological conditions or potentially alternative freezing/thawing procedures), on-site production requires the establishment of a certified facility within the hospital.

The use of human tissue-derived materials, although promising in terms of biological performance, presents challenges in sourcing the tissues, similar to organ shortages for transplant. Sackett et al.,[146] extracted human pancreas dECM from organs deemed unsuitable for transplantation, obtaining hydrogels that showed good cytocompatibility in vivo with various cell lines, and promising results in vivo. The authors argue that since 25% of the pancreas recovered for transplantation is found to be unstable for the purpose and discarded, they could be repurposed for dECM extraction and still find a medical application in different therapeutic approaches. Repurposing donated organs that turn out to be unsuitable for transplantation into the dECM would certainly be a positive way to honor the donation and still use the organ for therapeutic purposes. Regarding shortages, it must also be noted that compared to transplants, decellularized ECM could serve for treating several patients from the same source organ.

From a strictly regulatory perspective, building a bioink fully composed of human-derived hydrogels and cells would result in a tissue-engineered product following the ATMPs regulation in the EU and the RMAT designation for the FDA, moving away from the combination product definition and easing the regulatory process. Exceptions could be made if the regulatory bodies will define the carrier of the bioink and deposition mode as an integral part of the therapy, hence defining bioinks and bioprinted products as combinatory products.

Another way to overcome possible organ shortages is the extraction of c-dECM. This approach does not suffer from possible organ shortage issues, such as extracting dECM directly from donated organs, but might face difficulties in the scale-up of the production, costs, and final mechanical properties of the hydrogels. Overall, while the use of human tissue-derived biomaterials has shown some promising results, there is still a long way to demonstrate superior performance compared to animal-sourced dECM. Animal sourced materials are often easily available as byproduct waste in the food industry, and there are protocols in place to avoid disease transfer, since these materials have been used in the clinic for decades and are already covered by GMP procedures and standards (i.e., hyaluronic acid, gelatin, collagen). In general, the European market seems to favor the use of animal-derived products because of ethical and social unease toward the commercialization of human-based products. Consequently, processed allografts are less common in Europe and more readily available in the USA and China.[147]

5. Strategies to Ease the Regulatory Process

Despite all the challenges described, researchers and manufacturers have worked on ways to bring novel 3D-printed and hydrogel-based materials to the market and to facilitate the approval process. The milestones in the field leading to clinical trials of bioprinted implants are schematized in the timeline shown in **Figure 2**. Strategies to bridge the gap between research and market are discussed in this section.

The first way to ease the approval process of bioinks is to provide precise and standardized characterization paths and harmonize how hydrogels are tested. Researchers have advocated better and more specific standards for testing bioinks[148] and hydrogels in general, with clearer protocols and novel methods to test biocompatibility,[149,150] rheology of the prepolymer solutions,[77] viscoelasticity, and microstructure of the gels and their exposure to shear.[151] Martin-Saldaña et al.,[152] carefully reviewed characterization methods for hydrogels, dividing them into categories, such as chemical, mechanical, and thermal properties. Along with these methods, the authors reported the challenges related to the characterization of hydrogels, while covering techniques commonly used by researchers that could be a good starting point for drafting more specific regulations.

Wang et al.,[153] report an interesting point of view of the importance of providing better characterization during the entire life-cycle of the products; hence, they not only focused on pre-approval testing but also during post-market surveillance. While focusing broadly on medical devices, the authors also report examples of hydrogels referring that advancing analytical methods for post-market surveillance are needed to guarantee safety for the patients. With the continuous emergence of new hydrogel and cell therapies, introducing a classification system specifically addressing hydrogel and cell-based therapeutic products may help identify possible roadblocks in the approval process. Trubelja et al.,[154] proposed a novel classification system for hydrogels to consider their unique properties as materials while suggesting more targeted testing procedures. Hydrogels under clinical testing for cranio-facial applications were divided based on their complexity levels. Complexity was determined by a combination of the nature of the hydrogel therapeutic system, its composition, the presence or absence of cells, and the fabrication method. A matrix system was devised for the classification, which included the role of the FDA while providing examples of existing maxillofacial and dental products and how they would be categorized within the matrix. As the level of complexity within the proposed matrix increases, a progressive reduction of products is reported with only the Aurinovo (3DBioTherapeutics) product, which is classified as the most complex, involving bioprinting primary cells. Aurinovo is a 3D bioprinted implant for the reconstruction of the external ear in patients affected by microtia, which was approved for a phase I clinical study (pre-market approval obtained via 510(k)). The implant was built by harvesting the patients' chondrocytes with a biopsy, followed by expansion and bioprinting with a mirror geometry obtained from the scan of the healthy ear. The company envisioned to produce off-site the implant with a degradable shell to protect the cells while they remodeled the construct, and to allow for overnight cold shipping to the medical care facility after printing, assuming the complete liability over the implant.

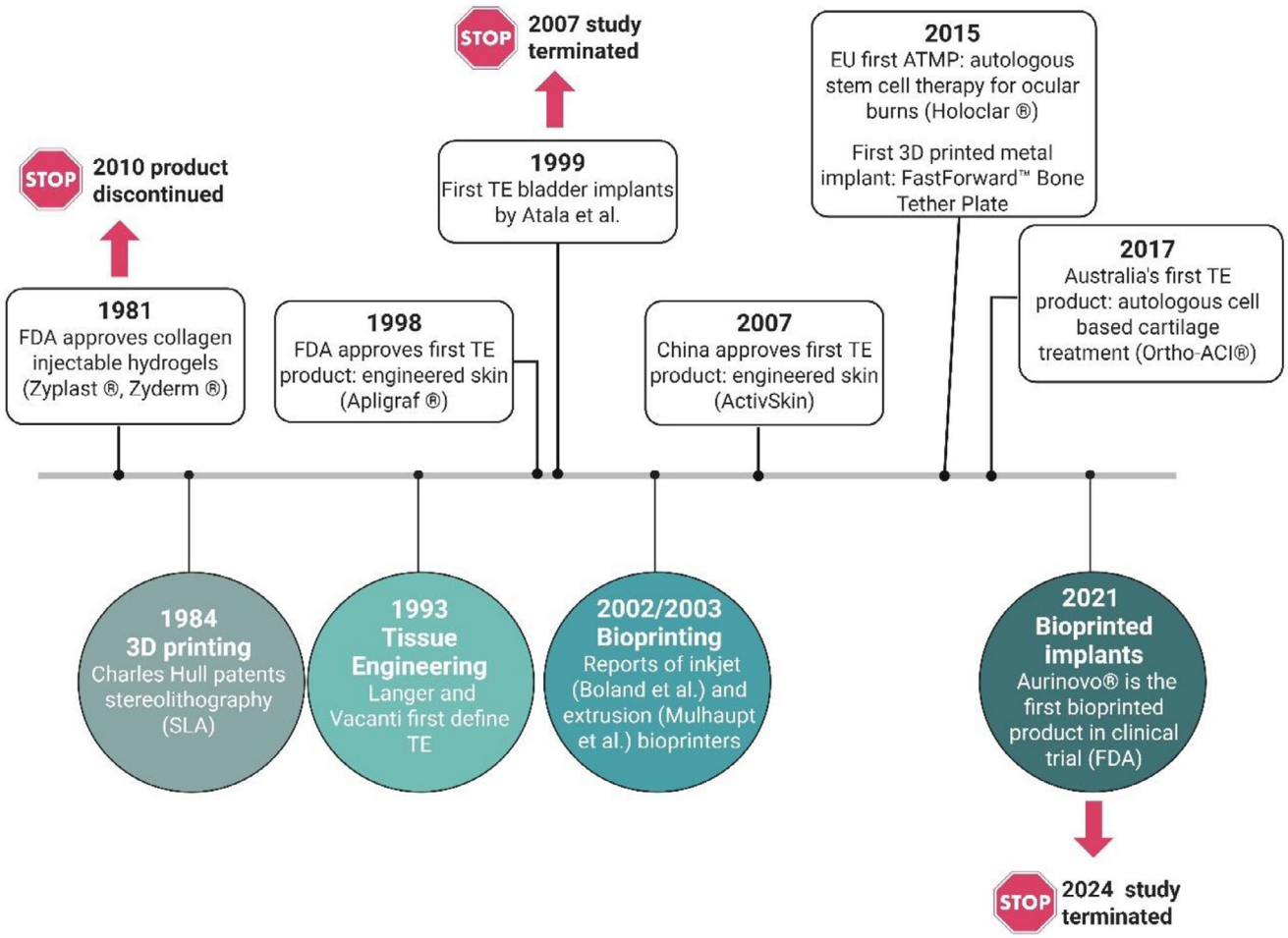

Figure 2. A timeline representing the most relevant milestones in the field of bioengineering that led to the first bioprinted constructs under clinical trials.

Trubelja et al.,[154] could not report any commercial application of products involving both the bioprinting of a hydrogel and the use of cells, which might indicate this as an obstacle. Being able to quickly identify limiting factors in the approval phase is the starting point to introduce innovation in devices, just up to the point that would block their approval. For example, Dimension Inx recently received FDA approval for its product CMFlex 3D, which is a 3D-printed composite hydroxyapatite and polylactide-co-glycolide bone graft. Bone grafts have interconnected porosity and microporosity, resulting in a highly absorbent and osteoinductive material. Due to the use of 3D printing, patient-specific devices can be fabricated. However, this would be more costly and challenging to approve, hence the company sells blocks of varying sizes, which are then cut into the desired shape by surgeons. This allowed them to obtain FDA premarket approval via the 510(k) pathway (similar to porous devices for bone grafting produced by the same company using different methods) as a Class (III) device and not as a personalized device. The company worked around the current regulatory market by tailoring its degree of complexity to fit into a category with easier approval and wider commercialization opportunities. They were also able to appeal to methods familiar to surgeons. It is not infrequent in orthopedics that materials are shaped in the operating room during surgery based on necessity (e.g., PMMA-based bone cement), and as a consequence, surgeons do not need additional training (in 3D printing, for example) to use this product or to dedicate additional time before surgery to organize the approval and 3D printing of the device. Providing a product that medical personnel are already trained to use greatly improves the chances for the product to be successfully marketed. Sacrificing a little novelty and complexity to take a product to the market faster can be beneficial both in terms of taking innovative solutions to patients faster and for a less risky post-market surveillance process.

Another strategy to eventually ease translation of bioprinting might require smaller and novel bioinks retailers to partner up with bigger companies that already are certified following GMP practices. This approach might result in a wider availability of certified products in the market and in knowledge transfer among companies on scaling up production processes and following standardized procedures. An example of this is the recent partnership between BioInx and Rousselot, which resulted in wider distribution of GMP grade gelatin and GelMA in the EU market.

An additional matter to consider is the strong possibility that when bioprinting is regulated, the bioprinting hardware will be

considered as a part of the combinatory product, since it is fundamental for its production. GMP compliant bioprinters have started to become available in the market, and their presence might be pivotal in providing novel opportunities to introduce bioprinting in clinical trials. An example is the NGB-C bioprinter from Poietis Biosystems, which is fully GMP compliant. The same company developed a bioprinted skin graft produced with the NGB-C, called Poieskin, fully bioprinted under GMP compliance, and showed promising results for skin regeneration in in vivo mouse models.[155] The company reports collaborations in place to commence clinical trials; however, the product is still not listed in the major clinical trial public databases (the EU Clinical Trials Register and the WHO International Clinical Trials Registry Platform).

A further step forward to aid translation to the clinic could be to couple the use of GMP compliant printing hardware with approved off-the-shelf cellularized bioinks. To achieve this, the production of cryopreserved cellularized bioinks has been investigated.[156] Cryopreservation is already used in several clinically approved allogeneic cell therapies, enabling the manufacture of bioink at specialized GMP compliant facilities and enabling its use in the clinic when required.

6. Future Perspectives

Bioprinting continues to emerge as a group of leading biofabrication technologies; however, the translation of bioprinted products to the clinic still faces obstacles. The difficulties arise from the fact that these products encompass novelties in the processing, materials, and combination with biological components, which complicates regulatory pathways.

While additive manufacturing has gained traction in the medical devices market, supported by ISO and ASTM standards, covering techniques such as powder bed fusion and patients-specific modeling, there is still a lack of a harmonized standard targeting the bioprinting of bioinks. These bioinks present a biphasic nature and viscoelastic behavior, making them impossible to characterize with standardized techniques already available for other materials, such as thermoplastic polymers and metals. Furthermore, the diversity of hydrogel sources (both natural and synthetic) and upstream chemical modifications needed for the preparation of bioinks for bioprinting with appropriate bioactivity makes the establishment of quality control systems and standardization complicated. Available standards on the characterization of hydrogels and natural sourced hydrogels are limited and not up to date with research. Research is currently converging, and techniques to characterize hydrogels will certainly allow harmonization and the establishment of new standards. This will favor universal terminology and a library of easily comparable literature results. A practical example on current standardization issues regards GelMA, one of the most widely used and synthesized natural-based hydrogels, also commercially available at the GMP grade. Nevertheless, there is no universal consensus on the way to express the degree of functionalization of GelMA,[157,158] making it hard to univocally compare results, which could be circumvented with a dedicated standard.

Standardization efforts in bioprinting are also advancing, particularly for EBB,[1] the most diffused bioprinting technique. Collaborative studies, such as the one by Grijalva Garces et al.,[159] demonstrate that challenges in reproducibility across 12 laboratories are still observed even when sharing the same SOP and bioinks to bioprint. Operator-dependent variables, such as manual calibration of the z-axis, affect the outcome. While there is a lot of literature on standardization of characterization of bioprinted constructs and selection of printing parameters,[72,73,75,160,161] to our knowledge, this is the only published study that targeted bioprinting reproducibility among different facilities and printers, providing tools and practical considerations that provide valuable insights for future standards.

The existence of harmonized and well-defined testing protocols is the first step toward easing the regulatory approval process. EMA, FDA, and NMPA regard hydrogels for TE and RM applications as combinatory products, due to the presence of cells and possibly tissue-derived products, resulting in a timeline for approval up to 10 years. The great potential to build personalized devices is currently not fully exploited, as both the use of patient-specific geometry and the presence of cultured cells in the medical device make the approval path harder. Regulatory bodies around the world set in place strategies to speed up the approval process for novel RM therapies, such as the RMAT designation from FDA, or the ATMP regulation in the EU. Some of these strategies have limitations, for instance in the USA the RMAT Fast-Track is limited to innovative therapies (cell-based therapies, tissue-engineering products, human cell/tissue-based products, or any combination of the aforementioned) addressing unmet clinical needs in the treatment of life threatening conditions.[154] Devices not falling in this restrictive category might benefit from the FDA's 510(k) pathway, if they can be demonstrated to be substantially equal to an already approved device. This tool allowed to introduce novel fabrication techniques to the market, such as 3D printing. For example, DimensionInx obtained the approval for CMFlex by the 510(k) pathway, demonstrating the substantial equivalence with two products already approved, OsteoScaf (by Texas Innovative Medical Devices (DBA) Skeletal) and Easy-Graft (by Guidor). The two predicate devices shared application and strong similarity in terms of composition and porosity, and the approval could be obtained by demonstrating comparable performance in terms of bone forming capacity in a canine critically sized dental defect. There have been concerns regarding this pathway restricting the novelty of the medical devices and posing health risks to patients, following evidence that the majority of the devices recalled for life-threatening effects had been approved through the 510(k).[162] The debate around regulations of medical device is complex, since variations and restrictions on the approval regulations have some cascade effects that can deeply impact the availability of medical devices. Kesavan et al.,[163] found a decline in venture capitalist investment in life sciences between 2009 and 2014, despite a global increase of investment in all industrial sectors in the same period. They linked this to the onset of stricter regulations for medical devices and uncertainty in the long timelines required to take products to the market, discouraging investors. The authors report that due to the funding difficulties and to a push toward comparative effectiveness research, low-cost medical devices and post-market gradual changes are getting more common. This leads to a process called "design drift" in which products are continuously subjected to minor changes and, finally, over the years,

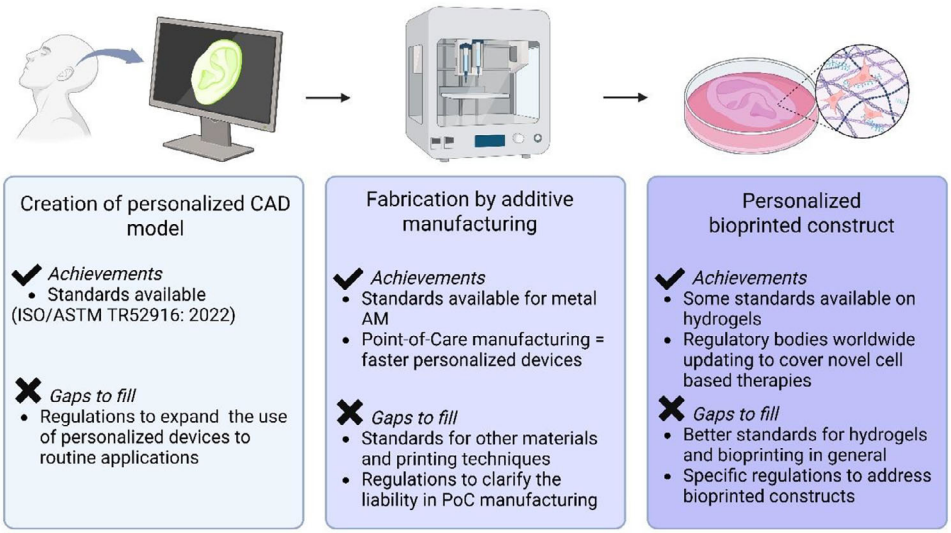

Figure 3. Simplified schematic of the major achievements and gaps to fill in the process of creating and translating a bioprinted construct to clinics.

become different than what was originally approved, raising safety issues and frequent reclaim cases.[162,163] The authors also argue that the comparative assessment methods for approval might not be suitable to properly assess the cost-effectiveness of an approach in longer periods, as this approach benefits short life-span studies and devices to promote cost-saving. Meanwhile, the approved devices used for the comparative studies are subjected to continuous changes, resulting in shorter post-Market surveillance time and overall, a global shorter monitoring time. This reflects a delicate balance: patient safety must never be compromised, yet investors worldwide lament the lengthy approval pathways,[164] and the resulting lack of funding and limited availability of novel medical devices can, in turn, pose risks to patients. Post-market surveillance is a powerful tool to evaluate the safety and market of medical devices and compensate for possible shortcomings from the pre-market approval process.[165,166] Unfortunately, collecting and comparing data for post-market quality control is challenging due to the existence of many different jurisdictions,[165] there is consensus in advocating for better harmonization of testing procedures around the globe to promote safety.

The regulatory bodies are making efforts to provide ways to bring novel RM (including bioprinting) to the clinic by organizing discussion boards with stakeholders and updating the existing approval pathways. Regardless, there is still a need for more specific testing procedures and regulations to accommodate the unique properties and variety of bioinks and bioprinting techniques. The approval of Aurinovo for clinical trials marks an important milestone for the market of bioprinted medical devices. Nevertheless, following the phase I clinical trial, the company decided to discontinue the product, stating that the decision was not driven by any safety-related concerns. As such, Aurinovo serves both as a demonstrator of the potential impact of bioprinted construct in clinics as well as the reflection of the challenges associated to their translation. These achievements also help to identify critical gaps that must be addressed in order to successfully translate bioprinting and bioprinted constructs to clinical practice beyond the compassionate use cases, as summarized in **Figure 3**.

Despite the remarkable progress of the bioprinting field, future developments might require similar approaches to those piloted by the 3D printing industry to create patient specific implants by addressing first compassionate cases. Furthermore, the evolution of bioprinting techniques and additional steps for upscaling of cell expansion are necessary through automated and manufacturing facilities that should be integrated either off- or on-site. Such facilities will certainly need to be adapted to ensure minimal operator dependent variables, GMP compliance, and installations in clean-rooms or surgical rooms equipped for the handling of the biological materials required for the preparation of bioinks.

Finally, several ethical considerations are of utmost importance as also evidenced by the previously covered domains of injectable hydrogels and tissue-engineered products. These considerations start to become analyzed in literature, extending beyond the biomaterials and cells used in the bioprinting process to include ethical implications of the resulting tissues or organs.[167,168] Moreover, social, cultural, and religious factors are gaining recognition of the ethical considerations surrounding bioprinting.[168,169] These are expected to evolve significantly as the technology advances and becomes integrated into clinics.

7. Conclusion

Advancements in bioprinting technologies hold promise for personalized medicine, tissue engineering, and in vitro modeling. However, the lack of harmonized standards, particularly for the combination of hydrogels and cells comprising bioinks, along with the bioprinting processes, remains a critical barrier for regulatory approval and subsequent translation.

Collaborative efforts in standardization, coupled with disruptive regulatory pathways such as the RMTA and the 510(k) initiatives, are gradually paving the way for a safer and more

efficient integration of these new technologies into healthcare. Despite of this, there is a long road to fully exploit the potential of these new approaches in both therapeutical and pharmaceutical applications that require continued research, cross-institutional collaboration, and continuous regulatory evolution.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biofabrication, bioprinting, clinical translation, regulatory, tissue engineering

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