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# Bespoke regulation for bespoke medicine? A comparative analysis of bioprinting regulation in Europe, the USA and Australia

Jane Nielsen*[,1,3], Jenny Kaldor[1], Adam Irwin[1], Cameron Stewart[2] & Dianne Nicol[1]

[1]Faculty of Law, University of Tasmania, Tasmania, Australia

[2]Faculty of Law, University of Sydney, Sydney, Australia

[3]ARC Centre of Excellence for Electromaterials Science, University of Wollongong, Wollongong, Australia

*Author for correspondence: Jane.Nielsen@utas.edu.au

Like most health-technology innovators, bioprinters are required to traverse a complex landscape featuring varied forms of regulation. This article focuses on one of the most complex aspects: the requirement imposed by regulatory authorities to satisfy them of the safety, efficacy and clinical utility of resultant healthcare products. Satisfaction of such requirements can result in a significant lag between 'breakthrough' and clinical delivery. This article examines this aspect of regulation in the USA, Europe and Australia, three leading bioprinting research jurisdictions. In particular, it examines medical devices and medicines categories of regulation, questioning whether a new approach to regulation is required or whether existing product-based regimes are sufficiently adaptive.

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Bioprinting is the application of 3D printing in the life sciences. If bioprinting lives up to its hype, it could revolutionize the way medicine is delivered. Popular media reports tout its potential for customized, in-clinic delivery in regenerative medicine and for addressing global organ shortages. Bioprinting is, in essence, a convergence of technologies, the aim of which is to produce human tissue. In some definitions, bioprinting includes the creation of external, or wearable, prosthetics. However, the definition used Groll *et al.* adopted in this article includes only implantable, not wearable prosthetics:

> *". . . the automated generation of biologically functional products with structural organization from living cells, bioactive molecules, biomaterials, cell aggregates such as micro tissues, or hybrid cell-material constructs, through bioprinting or bioassembly and subsequent tissue maturation processes"* [1].

Bioprinting brings many new tissue-engineering opportunities. At present, one of the main technological obstacles to the clinical translation of bioprinting is the development of effective bioinks [2]. A central challenge is ensuring the cells survive the printing process [3]. Further requirements include controlling cell proliferation and viability during and post printing [4], and achieving vascularization [5,6]. Some of these issues are common to tissue engineering using traditional methods, but others are more novel. Technological constraints continue to present numerous difficulties, making clinical application of bioprinting some way from realization [3].

Additionally, the manufacturing process for bioprinted products does not conform to traditional 'centralized' models of production in discrete manufacturing sites. Instead, manufacturing is dispersed or distributed across multiple production sites, including hospitals. The UK Government has coined the term 'redistributed manufacturing' to describe the diffuse mode of production that accompanies such technological advances [7,8]. Importantly for the purpose of this article, it further suggests that this shift in the way in which manufacturing occurs will necessitate a re-working of current regulatory schemes [8].

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Additional factors take this form of manufacturing further outside traditional, centralized models. One is the complexity of the design and manufacturing process, which includes a multitude of functions beginning with scanning and digital file development, and culminating in the printing of customized cells, tissue or body parts. Another is the broad range of actors involved in the manufacturing process, including designers, researchers, clinicians and manufacturing specialists based in hospitals or other locations.

Although much has been written about these material, biological and manufacturing particularities, each of which could potentially enhance or impede the translation of bioprinting technologies, there is less discussion about the regulatory environment itself. Like all innovative health technologies, clinical translation of the products and processes of bioprinting requires navigation through complex regulatory schemes, designed to safeguard patients' interests, but which undeniably slow the progress of products into the clinic. The focus of this article is therefore the adequacy of current regulatory schemes, and the mechanisms that are being put in place to deal with perceived inadequacies in these schemes.

## Why does bioprinting pose regulatory challenges?

Legal and other regulatory responses are often criticized for 'lagging' behind technological developments [9]. However, Lyria Bennett Moses argues that regulatory responses to new technologies should not be overly hasty but should be considered, responsive and forward looking. This requires careful consideration of regulatory mechanisms and actors in light of technological changes, in order to assess fitness for purpose. She further emphasizes the need to achieve institutional connectedness in order to avoid disciplinary siloing [10].

Bioprinting raises new regulatory challenges because of its use of novel processes to produce products that closely resemble those produced using more traditional tissue-engineering techniques. Researchers have pointed out that this may raise at least two clear categories of risks: first, novel manufacturing processes and the diffusion of manufacturing parties; and second, the unknown properties of bioprinted products (e.g., variability in strength and stability of scaffolds) [11]. Additional risks include those associated with different compositions of bioprinting materials. The use of bioinks is a case in point. Bioinks comprise cells, growth factors and materials (often hydrogels) to facilitate printing (usually extrusion) processes. In this sense they differ from materials used in tissue regeneration (that are not required to survive the printing process).

Generally speaking, one of the major motivations for government regulation is the management of unacceptable risks, in all their forms [12]. A core challenge for regulators is balancing risk management with freedom to innovate: ensuring that regulatory requirements do not stifle the development of products that will ultimately benefit consumers. This is particularly difficult in emerging technology areas where risks are uncertain. A precautionary approach to risk management advocates early, proactive, interventionist regulatory steps, even where evidence of risk is limited [13]. It has been argued that this approach is best embodied through the regulation of the processes that enable, rather than the products which result from, technological advancements [14]. As will be discussed below, however, some strongly disagree with this focus on process-based regulation [15].

Aligned with notions of risk is the concept of trust. Trust is an important ingredient in a regulatory system, and key to the social dimension of regulation. Effective regulation both relies on, and can engender, trust between regulators and regulated entities, which is an important aspect of responsive regulation [16]. Public trust in regulatory systems generates efficiencies because it is more conducive to compliance, and can 'free up' regulatory resources. However, research shows that trust is particularly fragile when there is a mix of public and private actors with competing interests [17] – as is the case in the bioprinting sphere, creating further regulatory challenges.

Finally, bioprinting also presents challenges to clinical product approval paradigms, which are currently being reshaped to accommodate safety concerns surrounding bioprinted products. These changes are important not only in order to ensure the safety of products, but also to maintain trust in bioprinting. Given the nascent stage of bioprinting technologies, reviewing whether it is necessary to implement regulatory changes becomes critical.

## Regulating bioprinting products

There is no doubt that the regulation of therapeutic goods, in the form of drugs, devices and biologics, is complex. Drugs and medical devices are generally positioned within distinct regulatory siloes. Combination products, incorporating more than one of these components, such as bioprinting products, further compound this complexity. This issue is not a new one: combination products have long challenged health regulation given their crossover into more than one regulatory scheme [18]. Early examples include tissue engineering, cell biology,

nanomedicine and gene therapy. The issues are underscored, however, by the arrival of bioprinting and the fact that many bioprinted products incorporate biological components.

Given the nascency of this technology and its novel production methods, some commentators have questioned whether medical regulators are equipped to deal with bioprinted products [19]. Although the US FDA has reported that it has interacted with a number of individuals using bioprinting techniques to print biological materials [20], there are currently no records of FDA approvals for 3D-printed biological products (or other regulatory authorities, for that matter). As such, we are not yet at the point where bioprinted products are close to being used clinically. Yet given the pace of technological development, it seems appropriate to use this juncture to ensure that the regulation of bioprinting technology is fit for purpose.

The development of any innovative health technology can be exposed to an extensive range of regulatory influences – a 'regulatory soup' [21]. The challenge is how to determine the most suitable forms of regulation – balancing patient safety and innovation. The unclear risks posed by new technologies like 3D-bioprinting demand a cautionary approach. But creation of an adequate evidence base to address these risks will inevitably delay their translation into the clinic. The remainder of this article focuses on one particular aspect of this regulatory environment: the requirement that all drugs, devices and related healthcare technologies are approved or otherwise listed by the relevant national regulatory body as being suitable for clinical application. This is universally recognized as the most onerous of all regulatory requirements in the healthcare context.

## Europe

In the European Union (EU), the European Medicines Agency (EMA), together with a network of regulatory authorities from member countries, is charged with responsibility for evaluating, supervising and monitoring medical products [22]. The EMA is actively promoting innovative policies aimed at creating adaptive pathways into the clinic [23]. As with the regulatory authorities in other jurisdictions, the EMA separates the regulation of medical devices from the regulation of drugs and biologics (which it refers to as medicinal products). The EU medical devices regime was significantly amended in May 2021 [24]. Medical devices are now regulated by the new Medical Device Regulation 2017/745 (MD Regulation), which replaced older medical devices regulations.

The EU regulatory regime for medicinal products is the Medicinal Products Directive 2001/83/EC and Regulation (EC) No. 726/2004. Medicinal products with biological components are brought within the scope of the Medicinal Products Directive by virtue of the Advanced Therapy Medicinal Products Regulation 2007 (ATMP Regulation). This Regulation applies to a range of advanced therapies including gene therapy, somatic cell therapy and tissue-engineered products. Recital 4 clarifies that combination products (that is, devices incorporating, for example, cell therapies) are also included within this regime, and as such it is applicable to most products of regenerative medicine. Bioprinted products are likely to be seen as sufficiently resembling regenerative medicine products (most likely tissue-engineered products) when considering which of these regulations applies [11]. Hence, device-cell therapy combination products will largely be regulated under this ATMP scheme.

However, products that contain cells or tissues will only be regulated under the ATMP scheme if they can be shown to have been 'engineered'. Article 2(C) of the ATMP Regulation requires that for products to qualify, they must have been subject to 'substantial manipulation' to achieve certain biological, physiological or structural properties or intended to achieve a function that differs from their original function (non-homologous use). It seems very likely that the derivation and expansion of cells for subsequent use in bioinks with a synthetic scaffold matrix will be sufficient to satisfy this first requirement for substantial manipulation [25]. One justification for this conclusion is that they do not obviously fit into the list of 'manipulations' in Annex 1 of the ATMP Regulation that are excluded from being 'substantial' manipulations (these include cutting, grinding, shaping centrifugation, cell separation, concentration or purification, sterilization and preservation). As such, products derived from manipulated cells, whether autologous or allogenic, are likely subject to the ATMP Regulation, provided the derived product meets the required threshold of undergoing substantial manipulation, or performing a new biological function [26]. However it should be noted that products containing cells that have not been substantially manipulated are instead regulated as transplants. Hence, bioprinted products derived from autologous cells, that fall short of being substantially manipulated, might possibly be classified as transplants rather than ATMP products [11].

Combined ATMPs are defined under Article 1(d) of the ATMP Regulation as products that incorporate a device component and a cellular or tissue component whose function is primary to the device component. In some instances, combination products may be subject to both the ATMP Regulation and the MD Regulation. Where the biological component is ancillary to the device, assessment takes place under Article 1(8) of the MD Regulation.


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But where the action of the biological substance is 'a principal and not ancillary' aspect of the device, Article 6 of the ATMP Regulation will apply. Even so, the medical devices component is still required to comply with device regulation requirements. It should be noted also that the embedding of software as a core component of bioprinting presents additional regulatory challenges, as software with a medical function is now deemed to be an active medical device pursuant to art 2(4) of the MD Regulation. As bioprinting moves toward the clinic, this has the potential to impose a significant regulatory compliance burden on software developers and users involved in bioprinting [27], of which they may not be presently cognisant [28].

Also important in the bioprinting context is the 'custom-made' device 'exemption' under the MD Regulation, which attributes a lower risk threshold to individualized devices made specifically to address the needs of a particular patient. The exemption was originally designed to apply to low-risk devices such as lenses and prosthetic limbs. This exemption was also featured in the preceding medical device directives. Article 2(3) of the MD Regulation exempts manufacturers from compliance with many of the stringent requirements in the Regulation on the basis that these individualized devices will not generally be placed on the market. Orthopaedic implants, for example, designed and made specifically for a particular patient, would seem to fall within the exemption despite ordinarily being classified as high-risk (class III) devices when mass produced [29]. However, the Regulation provides that products that are 'mass produced' and adapted, or mass produced using 'industrial manufacturing processes', will not be classified as custom-made devices. This would appear to limit the applicability of the exemption to many bioprinted products depending on how the terms 'mass-produced' and 'industrial manufacturing processes' are interpreted. There has been little guidance to date on these points, aside from confirming that 3D-printed devices will not qualify by default as custom-made devices and questioning the appropriateness of the custom-made device exemption to higher risk bioprinted products [30].

## Australia

Australian regulatory pathways have taken a similar course, modeled on the European experience. As with the European system, the Australian regulatory scheme has undergone recent revision: new regulations came into effect on 25 February 2021 [31]. Prior to this, devices with a biological component were regulated solely as biologicals.

All therapeutic goods, including devices, pharmaceutical products and biologics, are regulated in Australia under the Therapeutic Goods Act 1989 (Cth) (TG Act) and corresponding regulations. The Therapeutic Goods (Medical Devices) Regulations 2002 (Cth) (Device Regulations) specifically regulate devices. Biological products are included in the Therapeutic Good Regulations 1990 (Cth) (TG Regulations). Biologicals are defined in section 32A as products comprising, containing or derived from human cells or tissues. Regulation 2 of the TG Regulations defines biological medicines as medicines that are biologically derived vaccines, peptides, proteins or are polysaccharide based.

Recent amendments to the Device Regulations through the Therapeutic Goods Legislation Amendment (2019 Measures No. 1) Regulations 2019 (the 2019 TG Amendment) require regulation of device/cell combinations as class III medical devices. In addition, the 'viable and nonviable human origin components' of the device requiring assessment must be assessed for conformity with relevant regulatory requirements [32]. What this means is that, as in the EU, combination device-biological bioprinted products are now treated under the new Australian law as medical devices with a biological component. This change was seen as important to harmonize Australian law with that in other jurisdictions, including the EU, USA and Canada [32,33]. Interestingly, it has been noted that the requirement for separate assessment of the biological component has not been expressly incorporated into the recent amendment to the regulations [34]. However, it is likely that such an explicit amendment is not necessary.

Biologicals that form basic constituents of bioprinting products are already regulated as class III or IV biologicals: Regulation 2 of the 1990 TG Regulations provide that class II biologicals are biologicals that have been subjected to only minimal manipulation and are intended for homologous use. Regulation 3B stipulates that 'minimal manipulation' incorporates processes that result in no alteration to the biological characteristics, physiological functions or structural properties of human cells or tissues. In this respect, the scope of biological products that will fall within the ambit of cells or tissues that have been engineered is very similar in Australia and the EU.

There has been a real question in Australia as to whether bioprinted products containing a biological component are likely to be exempt from the requirements for high-risk devices, by virtue of the fact that they fit the definition of 'custom-made' medical devices. This exemption mirrors the European custom-made device exemption discussed above. However, recent changes through Regulation 4 of the 2019 TG Amendment remove high-risk, bioprinted products that are capable of reproduction from this definition of custom-made devices [35].

## The United States

In USA, the Code of Federal Regulations (Title 21 CFR), contains the regulations enacted under the Federal Food, Drug and Cosmetic Act governing the regulation of drugs, biologics and devices. Each is regulated by a different FDA office: the Center for Devices and Radiological Health (CDRH) for devices; and the Center for Biological Evaluation and Research (CBER) for biologics. The regulation of 'more than minimally manipulated' cells, tissues and cellular and tissue-based products (HCT/Ps) is undertaken via the biologics regulatory system, through the Public Health Service Act § 351 and its corresponding Human Cells, Tissues, and Cellular and Tissue-based Products Regulation (21 CFR Part 127). Through 21 CFR Part 1271(1)(f), 'minimal manipulation' for cells or nonstructural tissues means processing that does not alter biological characteristics. For structural tissue, minimal manipulation is defined as processing that does not alter the original characteristics relating to reconstruction, repair or replacement.

Combination products are specifically defined in 21 CFR §3.2(e) as comprising two or more regulated components that are combined and produced or sold as a single entity, with regulation being led by the agency responsible for the primary mode of action of the product (defined as the means by which a product achieves an intended therapeutic effect or action). The determination of the relevant mode of action for a particular product is triggered by the submission of a 'Request for Determination' by the manufacturer. In the case of most bioprinted products, it is likely that this would be the biological component of the product, given that the cellular constituent part would usually contribute to the therapeutic effect of the end product to the greatest extent [25]. A lack of predictability for developers and sponsors around designation of new combination products has led some commentators to propose an improved designation pathway model which introduces a granular test focusing on the primary intended use of the final product [36].

21 CFR does contain an exemption from the strict requirements outlined above for custom devices in section 520(b) of the Food, Drugs and Cosmetics Act. However, there are restrictive parameters around the operation of the exemption, most notably that the device must be designed to treat a unique pathology or condition that no other device is available to treat, and must be intended to meet the special treatment needs of either a physician or patient. A more recent amendment places further limits on the availability of the exemption [37]. The device must be used to treat a 'sufficiently rare condition' that would render clinical investigations impractical, and production of the device must be limited to 'no more than five units per year of a particular device type' [37]. The FDA has indicated that post-amendment, bioprinted products will not meet the requirements for the 'patient-matched' device design parameters contained in the legislation [38].

## Other relevant exemptions from standard regulatory pathways

While customized device exemptions exist in each jurisdictions discussed above, in each case, they might rightly be criticized for lack of clarity. For the most part, their intended operation has been fleshed out in policy documents that clarify they do not apply to high-risk 3D-bioprinted products. Even so, there are several other possible exemptions which lead to alternative regulatory pathways. In each of these instances, regulatory compliance with certain requirements must still be achieved, and responsibility for compliance generally rests with the manufacturer of the relevant device.

In the EU, for example, Article 28 of the ATMP Regulation contains a special access scheme for unapproved medical products, biologics and devices, which permits pre-authorization access to be granted to patients [39]. Article 5(5) of the MDR and Article 28(2) of the ATMP Regulation exempt hospitals and health institutions from many of the stringent regulatory standards for the preparation or manufacture of certain products. Qualification for the exemption is premised on a product meeting a number of requirements, namely: preparation on a nonroutine basis and nonindustrial basis; justification of unmet need, preparation according to specific quality standards; and use within the same member state, in a single hospital and under the exclusive responsibility of a medical practitioner. Reportedly, few products have actually been authorized by the MHRA under the ATMP exemption [11]. Despite this, the scope of the exemption has been criticized for lack of clarity in its use of the terms 'routine' and 'industrial' [11,34,40]. Moreover, the EU has acknowledged the very real possibility that the exemption may be used to circumvent regulatory requirements [41]. The MHRA has provided some guidance in relation to matters that will inform whether preparation of a product is routine, including the nature of the product(s) under consideration, and the scale and frequency of production [42].

Parallel (although not identical) special access schemes exist in the other jurisdictions. Under Australian legislation, there are three somewhat complex pathways under which access to unapproved therapeutic goods may be sought

through sections 18(1), 32CA(2) and 41HA of the TG Act; regulation 12A of the TG Regulations and regulation 7.2, Schedule 4 of the Medical Devices Regulations. Patients who are assessed as being 'terminally ill' (Category A) may be supplied with unapproved goods by their medical provider without TGA approval. Patients who do not meet this requirement (Category B) may be supplied with unapproved goods, but only with TGA approval.

The Category B exemption provides for patients with non-serious or life-threatening illnesses, and an unmet clinical need, to seek approval to access unapproved therapies. It could conceivably provide a path for those seeking access to personalized bioprinted products with a relatively low risk profile, although the threshold tests are higher than where a patient's condition is serious or life threatening. This aspect of the Australian system resembles the EU system [43], in that it allows access to special treatments where it would serve the interests of the patient. As in the EU system, there will invariably be interpretational difficulties in defining levels of seriousness and in establishing unmet need [44]. Despite this, the system is utilized relatively frequently in respect of both medicines and devices. It is difficult to identify with any precision the level of innovation inherent in devices that receive approval pursuant to Category B applications, and thus its applicability to bioprinted products.

Another route is via medical practitioners themselves: under the Authorised Prescriber Scheme, practitioners may apply to the TGA to supply specific unapproved goods to particular patients or groups of seriously ill patients on an ongoing basis.

An interesting recent development is the introduction by the Australian Parliament of an exemption for a 'medical device production system', which will permit the production, in hospitals, of low-risk medical devices without requiring compliance with the more onerous TGA device regulatory requirements faced by manufacturers. This exemption was introduced by the 2019 TG Amendment, Schedule 3, Part 1, Regulation 1.8. Clinicians involved in production at point of care will be exempted from being classed as manufacturers. Instead, manufacturers of medical device production systems, defined in Regulation 4 of the amending regulations as systems that consist of raw materials and main production equipment, are responsible for regulatory compliance. This provision has no parallel under the EU system (or any other international system), despite the fact that the ultimate aim of the device amendments is to achieve alignment with the EU approach, as noted in the Explanatory Memorandum to the 2019 TG Amendment.

The USA takes a narrower approach to granting special access to unapproved medicines and devices. According to 21 CFR § 312.305(a)(1), only patients with a serious or life-threatening illness can be granted access to investigational drugs, biologics and devices. Three potential pathways for investigational device exemptions (IDEs) exist under 21 CFR § 312.305(a)(1) to expand a particular clinical trial to include additional patients who satisfy certain criteria: emergency use, compassionate use for individuals or small groups and a treatment investigational device exemption, provided in 21 CFR § 812.36(a) [45]. Notably, compassionate use access is available both for devices that are being studied in clinical trials, and those that are not. In addition to the patient needing to have a life-threatening or serious condition, there are strict criteria for the grant of an IDE for compassionate use: there must be no alternative device available, and the benefits of using the investigational advice must outweigh the risks [45]. Again, criticism has been leveled at the imprecision with which the terms 'serious' and 'life threatening' have been defined, and the consequent lack of clarity as to the circumstances in which the exemption may be applied [44].

## Acting or reacting? product versus process-based regulation

As we have hinted, regulatory levers may be either process- or product-based. In theory, process-driven regulation is more proactive, whereas product-driven regulation is reactive. As noted by Joyce Tait and Les Levidow, proactive systems of regulation, based on the precautionary principle, attempt to avoid the manifestation of risks by operating before empirical evidence identifying those risks exists [13]. By contrast, reactive systems of regulation respond to scientifically established risks, and are "built up slowly, in a piecemeal fashion as new generations of product or process exhibit different hazards" [13].

In reality, systems of regulation are nuanced, and the linear categorization of proactive/process regulation and reactive/product regulation is not so clear cut. Product-based regulation can take a variety of forms, ranging from minimal oversight to mandatory screening that resembles the comprehensiveness of process-based regulation [13]. As a general rule, however, there are certain triggers for adopting process or product-based regulatory approaches, as indicated in Table 1.

Although product- and process-based regulation both assume the existence of some risk, they interpret the nature and source of risk differently. The question of what aspect of a product gives rise to risk is in large part

Table 1. Key assumptions of process- and product-based regulation.

| Process trigger | Product trigger |
|---|---|
| 1. A product created using a certain process poses risks, some of which may be unforeseeable<br>2. It is not possible to predict what these risks may be, given current knowledge; and<br>3. In order to minimize these risks, regulation should play a proactive role | 1. The risks associated with products created using new processes are not necessarily any greater than those associated with similar products created using more established processes; and<br>2. The reactive systems established to regulate these products (agriculture, food, therapeutic goods) can be adapted to manage these risks |

Adapted with permission from [13].

scientific. However, it also invokes epistemic questions as to the knowability and assessability of risks, and the role that regulation has in addressing them [46]. The central issue with bioprinting, from this perspective, is whether bioprinted products pose risks that are potentially greater than those associated with products produced using 'conventional' regenerative medicine techniques.

Similar debates regarding the appropriate focus for regulation have raged for many years in respect of genetically modified organisms (GMOs) and nanotechnology. In the GMO context, product-based regulation, which has been favored in Canada and USA, has as its focus "... the properties of the engineered organism, not the method by which it was produced" [47]. However, despite being favored by scientists and industry, product-based regulation has its share of detractors. For example, the notion of 'substantial equivalence' common to product-based regulatory systems has been criticized as unscientific and overly industry friendly [14,48].

Process-based regulation of GMOs also addresses the source of scientific risk, albeit in a less direct way. Arguably, conventional plant and animal breeding techniques have long histories of established use, which has led to a good understanding of the risks associated with them [49]. Because novel techniques lack this history, regulators are justified in imposing additional regulatory oversight measures until their risks are better understood. A very precautionary approach to regulating GMOs has been evident in the EU, exemplified by the imposition of "... regulatory oversight on all GMOs, from the trial stage of development onwards, without first requiring empirical evidence that such oversight is justified" [13].

One persistent question whether process-based systems are adequate to deal with future risks. As Marchant and Stevens have written:

> *"existing binary transgenic/conventional process-based regulatory systems in the US and EU will become increasingly stretched and scientifically undermined by trying to force the new technologies into their already outdated binary process-based regulatory frameworks. The new technologies will create a continuum of products that differ in potential risks by a variety of factors, of which process of production will increasingly become insignificant"* [50].

Product-based regulation makes it difficult to say with certainty whether technology is safe or not, as it may pose dangers in some contexts but not others [51]. The main difficulty with the product trigger, therefore, is establishing criteria for novelty that keep abreast of technological advancement.

It is usually thought that process-based systems inefficiently distribute the burdens of regulatory oversight because they do not discriminate (at least at the initial stage) between the types of products that will be subject to regulation [15]. Process-based regulation has the advantage of legislative specificity. Because it comprehensively captures a process, it is straightforward to collectively identify products for regulation. However, it may become difficult to amend regulations quickly enough to respond to technological change. A product trigger may lead to more devolved regulatory responsibility, as the evaluation of a product falls to whichever agency administers the product category to which it belongs. This could make the regulatory space more complex and difficult to navigate. Further, a product trigger would require assessment agencies to coordinate their regulatory approaches [52]. Failure to do this well could lead to regulatory duplication or gaps.

Finally, a regulatory system should not be based solely on scientific perceptions of risk: public acceptability also plays a role, and process-driven systems of regulation are argued to effectively permit the gradual development of scientific methods that mitigate risk and public concern [53]. We have already highlighted the importance of regulation as a tool to embody public trust. Scientific evidence is important, but should be supplemented by oversight which identifies the concerns of a diversity of stakeholders and citizens, as well as what strategies might allay those concerns, and which classes of products or processes should be scrutinised more closely by regulators [54]. Engendering trust in the quality of scientific expertise among multiple regulatory agencies in a product-based

system can present challenges [55]. In such cases, a process trigger may be more appropriate to ensure that each product receives adequate scrutiny.

As we have seen, the regulatory regimes for regenerative medicine in the jurisdictions examined take a very product-based approach to regulation. This reactive approach can be partially attributed to the length of time regenerative medicine has had to mature as a technology: the products of regenerative medicine closely resemble their naturally occurring counterparts, and the various technologies have been in existence for some time. However, the increasing stringency of regulatory measures in the EU relating to tissue engineering (particularly its categorisation as an advanced therapy), arguably also illustrates the difficulty for regulators in establishing clear technology 'zones' and responding to presently unknowable risks [56].

Similarly, medical device regulatory frameworks are currently heavily product focused. The regulation of bioprinted products will be considered under these product-based regimes, despite the fact that the products are generated using different processes to those using traditional tissue-engineering techniques – which may result in development of products with differing risk profiles. As we have seen, there has been a recent flurry of legislative activity around bioprinted products, to ensure that bioprinting products are captured by existing product regulation regimes, despite the fact that they are produced using different methods. These changes were implemented to close a perceived gap in the legislative regimes, which effectively exempted certain custom-made devices from the respective regimes.

The use of bioprinting processes may produce products with risk profiles that differ to those produced using traditional tissue-engineering techniques. These risks emanate from the challenges currently present in bioprinting research. They relate to the properties of new materials, combinations of materials used in bioprinting (which may derive from the composition of novel bioinks which need to remain viable through bioprinting) as well as the unknown effects wrought by the printing process – including risks associated with structural stability and batch-to-batch consistency [57]. The question is whether these potential risks are so significant that they require a departure from the standard regenerative medicine and medical device regulation pathways.

Some commentators have argued that uncertainty about how bioprinting will be used in future medicine warrants a precautionary, process-based system of regulation for bioprinted products [11]. This would necessarily involve imposing either an alternative model to the product-based model outlined in the previous section, or an additional, bespoke layer of regulation, most likely at the preclinical phase. It might require the implementation of new legal requirements, or the integration of ethics considerations at the early research phase, so that scientists and ethicists are in constant communication (for example the Responsible Research and Innovation approach increasingly common in nanotechnology and synthetic biology) [58].

Certainly, there is considerable merit in embedding ethics considerations at the beginning of a product's life-cycle, preferably early in the research phase. The availability of such ethics expertise would, in theory, prompt scientists to be mindful of ethical considerations at the research and design stage. Cementing practices that entrench ethical behaviors will go a long way toward ensuring bioprinted products are developed in as comprehensively safe a manner as possible.

However, other commentators consider that the disruptive potential of bioprinting may have been overstated, and that existing legal frameworks may be adequate to ensure the safety and efficacy of bioprinted products [40]. Although not as 'cautious' as a process-based system, we argue that the current product-based systems for regulating devices with a biological component are *precautionary* enough to provide adequate safeguards to ensure product safety and efficacy, while at the same time allowing innovation to proceed. The governance models in Europe and Australia share many common aspects. The definition and treatment of biologics is consistent across jurisdictions, as is the treatment of devices and combination products. There is some divergence in relation to the applicability of exemptions for custom-made devices and other alternative pathways, and it remains to be seen how these divergences play out in future. There will undoubtedly be a need to reconsider the regulatory landscape as these pathways are tested.

Particularly in Europe and Australia, considerable consultation has shaped recent developments and enabled industry input into the evolution of governance regimes. This level of precaution seems appropriate at the current time, given the inherent uncertainties associated with early-stage clinical translation. However, as the technology evolves and clinical translation moves closer to reality, regulatory requirements will need to continue to evolve in parallel and be responsive to industry, clinical and community demands. Although it may not provide the degree of certainty that a process-driven model might provide, the pace of technological innovation demands more rapid regulatory response. This responsive approach will, in turn, engender public and industry trust in the regulatory

process, an outcome that is critical to acceptance of the capacity of regulatory agencies to regulate for safety while encouraging innovation.

How might this be achieved? We argue that the extant product-based schemes have already proved capable of integrating elements of public participation, accountability and transparency, all core pillars in engendering trust among stakeholders, in regulating for health innovation [59]. As stated above, all of the regulatory agencies surveyed in this paper have been cognizant of employing consultative models in enacting recent regulatory reforms, and in ensuring an iterative developmental approach. Public, expert and policy input and debate into proposed regulatory reforms has been sought and incorporated. A participatory model of regulation relies on scientific expertise, but makes explicit the cultural and normative assumptions on which those assessments rely [60], and takes into account other forms of knowledge important to positive regulatory outcomes [61]. It also attempts to account for the many other normative considerations inherent in the use of a new technology. Because the technologies at issue in this paper are at such an early stage of development, the plethora of values likely to be impacted through their development and use cannot yet be exhaustively identified.

The challenge from here will be to ensure that stakeholder input continues to be an integral component at subsequent stages of the development and application of these regulatory schemes, and in regulatory decision-making [62]. Acknowledgement of the normative considerations and the many interests and values impacted by emerging health innovations is a critical aspect of regulatory development, and should not be dispensed with in favor of sole reliance on linear assessments of risk versus benefit. Given the highly personalized nature of bioprinted products, establishing effective feedback loops by adopting meaningful public participation strategies and incorporating individual as opposed to population-level data, will be paramount to achieving strong regulatory outcomes.

## Conclusion

There is no doubt that bioprinting technologies will present a host of issues for therapeutic goods regulators. This much has been recognized by responsible agencies, and accounts for the recent flurry of legislative activity around the world. Recent regulatory amendments in Europe, Australia and USA have clarified that bioprinted products need to satisfy biological and medical device regulatory requirements.

The potential for the mass customization of bioprinted products, combined with dispersed production chains, mean that questions arise in respect of these traditional pathways for regulating medical devices, and whether the traditional product-based regulatory schemes in operation will be sufficient. The question here is what challenges to governance are raised by bioprinting. It has been suggested that the risks that arise from the use of bioprinting are due to the difference in processes used to produce products that may otherwise be produced by traditional tissue-engineering approaches. This suggests that a process-based regulatory approach might be more appropriate in the long term.

Conversely, the parallels between tissue engineering using traditional techniques, and engineered tissue using bioprinting methods, supports their regulation through the same pathways. Although bioprinting may give rise to risks that are as yet unforeseeable, there is no reason at this point to think these risks will not be resolved. As such, despite the attraction of process-based regulation, it may be more appropriate to maintain the current product-based approach at the present time. To take the next step of implementing a bespoke system of regulation at this early stage of the technology's development may have the unwanted effect of discouraging innovation in an industry that has already had to come to grips with considerable recent regulatory activity aimed at bringing it in line with more traditional technologies. There can be little doubt, however, that the adoption of a more adaptive and responsive approach to regulation is critical in assessing the risk profile of a rapidly evolving technology such as bioprinting, and would ultimately result in greater public and stakeholder trust.

## Future perspective

In the next 5–10 years, bioprinted products will increasingly be making their way through the clinical translation pipeline. Although each new product will raise its own specific risks, a number of the safety and efficacy concerns associated with bioprinted products will have been resolved. There will be significant potential for societal benefit. In order to ensure that this benefit is fully realized, it will be crucial to assess the adequacy of current regulatory requirements and to explore different approaches to regulation. The current conceptualization has steadily evolved from a state-centred or 'command-and-control' theory of regulation [54], to become gradually more participant centric.


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Various scholars in regulatory theory have rejected traditional command-and-control models of regulation as too prescriptive and inflexible, particularly when it comes to the regulation of rapidly evolving innovative technologies. Their approaches to the topic range from Ayres and Braithwaite's responsive regulation [16], to Black and Baldwin's risk-based regulation [63], to more recent conceptions of adaptive and other forms of regulation [64]. In each case, state-centred regulation is rejected in favor of more broadly defined conceptions of regulation that include a wider scope of influences on the behavior of actors.

The concepts of 'regulatory pluralism' and 'networked governance', as espoused by Ayres and Braithwaite [16], Gunningham and Grabosky [65], Black [12], Parker [66] and others, capture these decentred forms of regulation. Decentred regulation thus connotes a web of interdependent regulatory actors who work cohesively to achieve a desired regulation outcome. Proponents of decentred regulation reject purely 'state institutional governance' in favour of less hierarchical and more egalitarian modes of regulation.

These adaptive approaches to regulation have being discussed extensively in the context of governance of health policy more broadly, particularly in Europe. This type of adaptive governance model incorporates useful features such as polycentricity, collaboration, incrementalism, flexibility, anticipation, reflexivity and responsiveness [67]. It is timely to explore how adaptive and other forms of regulation might be applied in the context of the clinical translation of bioprinted products.

## Executive summary

- This article examines the regulatory requirements for clinical translation of the products and processes of bioprinting.

**Why does bioprinting pose regulatory challenges?**

- A core challenge for regulators is to ensure that regulating for risk is balanced with freedom to innovate: that regulatory requirements do not operate to stifle the development of products that will ultimately benefit consumers.
- This is problematic in emerging technology areas where risks are uncertain.

**Regulating bioprinting products**

- Drugs (including biologicals) and medical devices are generally positioned within distinct regulatory siloes.
- Combination products, such as bioprinting products, incorporate more than one of these components.
- Recent amendments to the regulatory requirements in Europe, Australia and USA mean that bioprinted products are regulated as biologicals and devices.
- Exemptions for custom-made devices lack clarity in each jurisdiction.

**Acting or reacting? product- versus process-based regulation**

- It has been argued that a process-based approach may be more appropriate where risks are uncertain.
- However, although not providing as 'cautious' an approach as a process-based system, the current product-based system for regulating devices with a biological component provides adequate safeguards to ensure product safety and efficacy, while at the same time allowing innovation to proceed.
- A responsive and adaptive regulatory approach is desirable as bioprinting advances into the clinic.
- Governance models should be capable of taking into account the diversity of normative value inherent in development and delivery of innovative healthcare technologies.

**Conclusion**

- Bioprinting technologies present a host of issues for therapeutic goods regulators, which to date have been resolved through product-based regulatory approaches.
- Despite the attraction of process-based regulation, it appears more appropriate to maintain the current product-based approach at the current time.
- However, over time regulation will need to become more responsive and adaptive to meet societal needs.

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## References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Groll J, Boland T, Blunk T *et al.* Biofabrication: reappraising the definition of an evolving field. *Biofabrication* 8(1), 013001 (2016).
2. Ji S, Guvendiren M. Recent advances in bioink design for 3D bioprinting of tissues and organs. *Front. Bioeng. Biotechn.* 5, 23 (2017).
3. Atala A, Forgacs G. Three-dimensional bioprinting in regenerative medicine: reality, hype, and future. *Stem Cells Transl. Med.* 8(8), 744–745 (2019).
4. Skeldon G, Lucendo-Villarin B, Shu W. Three-dimensional bioprinting of stem-cell derived tissues for human regenerative medicine. *Philos. Trans. R. Soc. B* 373(1750), 20170224 (2018).
5. Eswaramoorthy S, Ramakrishna S, Rath SN. Recent advances in three-dimensional bioprinting of stem cells. *J. Tissue Eng. Regen. Med.* 13(6), 908–924 (2019).
6. Derakhshanfar S, Mbeleck R, Xu K, Zhang X, Zhong W, Xing M. 3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances. *Bioactiv. Mater.* 3(2), 144–156 (2018).
7. Pearson H, Noble G, Hawkins J. Redistributed Manufacturing Workshop Report. Engineering and Physical Sciences Research Council, UK (2013). https://epsrc.ukri.org/newsevents/pubs/re-distributed-manufacturing-workshop-report/
8. Phillips W, Medcalf N, Dalgarno K *et al.* Redistributed manufacturing in healthcare: creating new value through disruptive innovation. Redistributed Manufacturing in Healthcare Network White Paper, Bristol, UK (2018). http://rihn.org.uk/wp-content/uploads/2018/01/RiHN_WP_Full_double_web.pdf
9. Bennett Moses L. Recurring dilemmas: the law's race to keep up with technological change. *Univ. Ill. J. Law Technol. Policy*. Spring (2007).239–286
10. Bennett Moses L. Agents of change: how the law 'copes' with technological change. *Griffith Law Rev.* 20(4), 763–794 (2011).

•• **Analyses the relationship between technology and law, and overviews the Australian landscape for legal change in the face of technological advancement.**

11. Li P, Faulkner A, Medcalf N. 3D bioprinting in a 2D regulatory landscape: gaps, uncertainties, and problems. *Law Innov. Technol.* 12(1), 1–29 (2020).

•• **Provides a comprehensive analysis of the European regulatory regime and identifies gaps and current ambiguities.**

12. Black J. Critical reflections on regulation. *Aust. J. Leg. Philos.* 27, 1–36 (2002).
13. Tait J, Levidow L. Proactive and reactive responses to risk regulation. *Futures* 21(5), 219–231 (1992).

• **Examines various prompts for the choice of adoption of product versus process regulation.**

14. Kysar DA. Preferences for processes: the process/product distinction and the regulation of consumer choice. *Harv. Univ. Law Rev.* 118(2), 525–642 (2004).
15. Tagliabue G. Product, not process! Explaining a basic concept in agricultural biotechnologies and food safety. *Life Sci. Soc. Policy* 13, 3 (2017).
16. Ayres I, Braithwaite J. *Responsive Regulation: Transcending the Deregulation Debate*. Oxford University Press, Oxford, UK (1994).

• **Argues for adaptive regulation and proposes a seminal model for embodying adaptive regulation, emphasizing the importance of public trust.**

17. Critchley C, Nicol D. Commercialisation of genomic research: the issue of public trust. In: *Tensions and Traumas in Health Law*. Freckleton I, Petersen K. (Eds)., 350–384 Federation Press, Sydney, AU (2017).
18. Bartlett Foote S, Berlin RJ. Can regulation be as innovative as science and technology? The FDA's regulation of combination products. *Minn. J. Law Sci. Technol.* 6(2), 619–644 (2005).
19. Wolinsky H. Printing organs cell-by-cell. *EMBO Rep.* 15(8), 836–838 (2014).
20. Di Prima M, Coburn J, Hwang D, Kelly J, Khairuzzaman A, Ricles L. Additively manufactured medical products – the FDA perspective. *3D Print. Med.* 2(1), 1 (2016).
21. Nicol D, Bubela T, Chalmers D *et al.* Precision medicine: drowning in a regulatory soup? *J. Law Biosci.* 3(2), 281–303 (2016).
22. European Medicines Agency. The European regulatory system for medicines: a consistent approach to medicines regulation across the European Union. London, UK (2016). https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf
23. Nicotera G, Sferrazza G, Serafino A, Pierimarchi P. The iterative development of medicines through the European Medicine Agency's adaptive pathway approach. *Front. Med.* 6, 148 (2019).

24. Kritikos M. 3D printing for medical and enhancement purposes: legal and ethical aspects. European Parliamentary Research Service, In-depth Analysis: Science and Technology Options Assessment (2018) https://www.europarl.europa.eu/RegData/etudes/IDAN/2018/614571/EPRS_IDA(2018)614571(ANN2)_EN.pdf

25. Hourd P, Medcalf N, Segal J, Williams DJ. A 3D-bioprinting exemplar of the consequences of the regulatory requirements on customized processes. *Regen. Med.* 10(7), 863–883 (2015).

•• **Provides a detailed overview of USA and European regulatory scheme impacting on customized 3D-printed devices, and highlight deficiencies.**

26. European Medicines Agency. Reflection paper on classification of advanced therapy medicinal products. London, UK (2015). https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf

27. European Commission. Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR. Medical Devices Coordination Group, Brussells, Belgium (2019) https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2019_11_guidance_qualification_classification_software_en.pdf

28. Bicudo N, Faulkner A, Li P. Software, risks and liabilities: ongoing and emergent issues in 3D bioprinting. *J. Risk Res.*10.1080/13669877.2020.1848904 (2020).

29. Willemsen K, Nizak R, Noordmans HJ, Castelein RM, Weinans H, Kruty MC. Challenges in the design and regulatory approval of 3D-printed surgical implants: a two-case series. *Lancet Digit. Health* 1(4), 163–171 (2019).

30. European Commission. Questions and answers on custom-made devices. Medical Devices Coordination Group, Brussells, Belgium (2021). https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-3_en.pdf

31. Therapeutic Goods Administration. Custom made medical devices: information for sponsors, health professionals & manufacturers. Department of Health, Canberra, Australia (2021). https://www.tga.gov.au/custom-made-medical-devices

32. Therapeutic Goods Administration. Consultation: proposed regulatory scheme for personalised medical devices, including 3D-printed devices. Department of Health, Canberra, Australia (2019). https://www.tga.gov.au/sites/default/files/consultation-proposed-regulatory-scheme-personalised-medical-devices-including-3d-printed-devices.pdf

33. Therapeutic Goods Administration. Consultation Paper: proposed regulatory changes related to personalised and 3D-printed medical devices. Department of Health, Canberra, Australia (2017). https://www.tga.gov.au/sites/default/files/consultation-proposed-regulatory-changes-related-personalised-and-3d-printed-medical-devices.pdf

34. Horst A, McDonald F. Uncertain but not unregulated: medical product regulation in the light of three-dimensional printed medical products. *3D Print. Addit. Manuf.* 7(5), 248–257 (2020).

•• **The authors set out aspects of regulatory regimes for 3D-printed medical products in USA, Europe and Australia and analyze regulatory coverage.**

35. Theraputic Goods Administration. Personalised medical devices (including 3D-printed devices): regulatory changes for custom-made medical devices. Department of Health, Canberra, Australia (2021). https://www.tga.gov.au/sites/default/files/personalised-medical-devices-including-3d-printed-devices.pdf

36. Uemura N, Kasanuki H, Umezu M. New visualization models of designation pathway and group categorization of cell-device and protein-device combination products in the United States. *Therap. Innov. Regul. Sci.* (2021).

37. Food and Drug Administration. Medical devices; custom devices; technical amendment. 81 FR 70339, US Department of Health and Human Services, Silver Springs, MD, USA (2016).https://www.federalregister.gov/documents/2016/10/12/2016-24438/medical-devices-custom-devices-technical-amendment

38. Food and Drug Administration. Technical considerations for additive manufactured medical devices: guidance for industry and Food and Drug Administration staff. US Department of Health and Human Services, Centre for Biologicals Evaluation and Research, MD, USA (2017). https://www.fda.gov/files/medical%20devices/published/Technical-Considerations-for-Additive-Manufactured-Medical-Devices---Guidance-for-Industry-and-Food-and-Drug-Administration-Staff.pdf

39. Deloitte. Patient access to innovative medicines in Europe: a collaborative and value based approach. (2019). https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-patient-access-to-innovative-medicine-in-europe.pdf

40. Tsyuki K, Yano K, Watanabe N, Aruga A, Yamato M. Compassionate use of drugs and medical devices in the Unites States, the European Union and Japan. *Regen. Therap.* 4(1), 18–26 (2016).

41. European Commission. Report From the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Brussels, Belgium (2014). https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2014:0188:FIN:EN:PDF

42. Medicines and Healthcare Products Regulatory Agency. Guidance on 'non-routine'. Department of Health and Social Care, London, UK, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf

43. Walker MJ, Rogers WA, Entwistle V. Ethical justifications for access to unapproved medical interventions: an argument for (limited) patient obligations. *Am. J. Bioeth.* 14(11), 3–15 (2014).

44. Von Tigerstrom B, Harris E. Access to experimental treatments: comparative analysis of three special access regimes. *J. Law Med.* 24(1), 119–149 (2016).
45. Food and Drug Administration. Expanded access for medical devices. US Department of Health and Human Services, Silver Springs, MD, USA (2019). https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices-compassionate
46. Gupta A. Governing trade in genetically modified organisms: the Cartagena protocol on biodiversity. *Environ. Sci. Policy Sustain. Dev.* 42(4), 22–33 (2000).
47. National Academy of Sciences. *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*. National Academy Press, DC, USA (1987).
48. Millstone E, Bunner E, Mayer S. Beyond 'substantial equivalence'. *Nature* 401(6753), 525–526 (1999).
49. McLean MA, Charest P. The regulation of transgenic trees in North America. *Silvae Genet.* 49(6), 233–239 (2000).
50. Marchant G, Stevens Y. A new window of opportunity to reject process-based biotechnology regulation. *GM Crop. Food* 6(4), 233–242 (2015).

- **The authors critique the process-based regulation that has characterized governance of genetically modified organisms.**

51. Alta Charo R. The legal and regulatory context for human gene editing. *Issues Sci. Technol.* 32(3), (2016). https://issues.org/the-legal-and-regulatory-context-for-human-gene-editing
52. Eckerstorfer M, Engelhard M, Heissenberger A, Simon S, Teichmann H. Plants developed by new genetic modification techniques – comparison of existing regulatory frameworks in the EU and non-EU countries. *Front. Bioeng. Biotechnol.* 7, 32 (2019).
53. Faunce T, Ray A, Gardiner C, Preiss T, Burgio G. Regulating RNA research and CRISPR gene drives to combat biosecurity threats. *J. Law Med.* 26(1), 208–213 (2018).
54. Kuzma J. Reboot the debate on genetic engineering. *Nature* 531(7593), 165–167 (2016).
55. McHughen A. A critical assessment of regulatory triggers for products of biotechnology: product vs. process. *GM Crop. Food* 7(3–4), 125–158 (2016).
56. Faulkner A, Kent J, Geesink I, FitzPatrick D. Purity and the dangers of regenerative medicine: regulatory innovation of human tissue-engineered technology. *Soc. Sci. Med.* 63(9), 2277–2288 (2006).
57. Bian L. Functional hydrogel bioink, a key challenge of 3D cellular. *APL Bioeng.* 4(3), 030401 (2020).
58. Vermeulen N, Haddow G, Seymour T, Faulkner-Jones A, Shu W. 3D bioprint me: a socio-ethical view of bioprinting human organs and tissues. *J. Med. Ethics* 43(9), 618–624 (2017).
59. Joss S. Introduction: public participation in science and technology policy- and decision-making – ephemeral phenomenon or lasting change? *Sci. Public Policy* 26(5), 290–293 (1999).
60. Jasanoff S. Technologies of humility: citizen participation in governing science. *Minerva* 41(3), 223–224 (2003).
61. Faulkner A, Poort L. Stretching and challenging the boundaries of law: varieties of knowledge in biotechnologies regulation. *Minerva* 55(2), 209–228 (2017).
62. Taylor L. Public actors without public values: legitimacy, domination and the regulation of the technology sector. *Philos. Technol.*https://doi.org/10.1007/s13347-020-00441-4 (2021).
63. Black J, Baldwin R. Really responsive risk-based regulation. *Law Policy* 32(2), 181–213 (2010).
64. Marchant G, Abbott KW, Allenby B. *Innovative Governance Models for Emerging Technologies*. Edward Elgar, Cheltenham, UK (2013).
65. Gunningham N, Grabosky P. *Smart Regulation: Designing Environmental Policy*. Oxford University Press, Oxford, UK (1998).
66. Parker C. The pluralization of regulation. *Theor. Inq. Law* 9(2), 349–369 (2008).
67. Kickbusch I, Gleicher D. Governance for health in the 21st century. World Health Organization Europe, Copenhagen, Denmark (2009). https://www.euro.who.int/__data/assets/pdf_file/0019/171334/RC62BD01-Governance-for-Health-Web.pdf