3D bioprinting in a 2D regulatory landscape: gaps, uncertainties, and problems

Article (Accepted Version)

Li, Phoebe, Faulkner, Alex and Medcalf, Nicholas (2020) 3D bioprinting in a 2D regulatory landscape: gaps, uncertainties, and problems. *Law, Innovation and Technology*, 12 (1). pp. 1-29. ISSN 1757-9961

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/78577/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

3D bioprinting in a 2D regulatory landscape: gaps, uncertainties, and problems

Phoebe Li^{a*}, Alex Faulkner^b, Nicholas Medcalf^c

^a School of Law, Politics, and Sociology, University of Sussex, Falmer, Brighton, BN1 9QE, UK. Email: Phoebe.Li@sussex.ac.uk; ^b Centre for Global Health Policy, University of Sussex, UK; ^c EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, Loughborough University, UK

Notes on contributors

Phoebe Li is Senior Lecturer in Law at the University of Sussex, UK.

Alex Faulkner is Professor in Sociology of Biomedicine & Healthcare Policy, University of Sussex, UK.

Nicholas Medcalf is Visiting Professor of Regenerative Medicine Manufacture at Loughborough University, UK.

3D bioprinting in a 2D regulatory landscape: gaps, uncertainties, and problems

ABSTRACT

In this paper we assess both the *ex ante* and the *ex post* dimensions of the regulatory landscape of 3D bioprinting governance. While the former is mainly concerned with the market approval and safety of 3D bioprinting, the latter is concerned with the matter of liability once bioprinting has been licensed or authorised for use. In this 2D landscape, we highlight three sets of choices: whether regulation should focus on the process, the product or both; whether to rely on existing regimes or create a new bespoke and distinct regulatory framework; and whether to employ top down, bottom up, or co-regulation. We identify a series of interpretative uncertainties as well as gaps in the current legal regimes. We consider an initial provisional ‘process-based’ approach and a co-regulation model for bioprinting governance. We anticipate that the study of the regulatory landscape will offer key insights in relation to other types of biofabrication.

KEYWORDS: Redistributed Manufacturing (RDM), mass customisation, bioprinting, co-regulation, ATMP, medical device

LIST OF FIGURE:

Table 4.3. Biofabrication regulatory scenarios

1. Introduction

Additive manufacturing (AM), also known as 3-Dimensional printing (3D printing, or 3DP), has disrupted traditional industrial business models by introducing Computer Aided Design (CAD) into Computer-Aided Manufacturing (CAM). In so doing, manufacturing could be re-distributed to dispersed sites potentially at a lower cost. As opposed to conventional subtractive

production methods, 3D printing works by adding multiple layers of materials to form an object as instructed by CAD/CAM,¹ and the intrinsic properties especially the strength and quality of products can be compared to conventional subtractive manufacturing products. Standardisation of 3DP may be able to delineate acceptable boundaries of risks and responsibilities that arise,² however, in the context of risk regulation, it is currently still unclear whether a product made via AM should be deemed as equivalent to their conventional counterparts.

3D printing has been widely used by grass-roots DIY communities to repair and reprint spare parts of physical objects,³ and although it is not our focus here, the association of the field with open source software and democratic user movements is important to note,⁴ and a principle of local production and control is of general, broader application. Bioprinting adapts 3D printing technologies to biomedical products including living cells. Its applications in human tissue engineering and regenerative medicine (RM) are known as 3D bioprinting (or just ‘bioprinting’) promoting an ambitious vision of repairing and reproducing human cells, tissues, and body parts locally and on demand.⁵ Most bioprinted medical products will be categorised as ‘Advanced Therapy Medicinal Products’ (ATMPs) in the EU/UK, which form a large part of ‘regenerative medicine’ that aims to provide medical treatments through human tissue and cell-based products.⁶

It is anticipated that diffused production in 3D bioprinting will greatly facilitate the preservation of starting and intermediate materials and the final product by shortening the

¹ Hod Lipson and Melba Kurman, *Fabricated: The New World of 3D Printing* (John Wiley & Sons. Inc., 2013) 65-84.

² *ibid*, 222-223.

³ John Hornick, *3D Printing Will Rock the World* (CreateSpace Independent Publishing Platform, 2015) 53.

⁴ Carla Palavicino and Kornelia Konrad, ‘Doing is Believing: How Material Practices Shape the Future in 3D Printing’ in Diana M. Bowman et al. (eds) *Practices of Innovation and Responsibility: Insights from Methods, Governance and Action* (AKA/IOS Press, 2015) 141-163.

⁵ Lipson and Kurman (n 1) 111-128; Chee Kai Chua and Wai Yee Yeong, *Bioprinting: Principles and Applications* (World Scientific Publishing, 2015).

⁶ Phoebe Li and Alex Faulkner, ‘3D Bioprinting Regulations: a UK/EU Perspective’ (2017) 8 *European Journal of Risk Regulation* 441-447. See Section 3.2.1.

distance between the manufacturer and the consumer, solving problems of degradation of live biomaterials during transit times between producers and hospital and patient. Such a dispersed model of production is termed ‘Redistributed manufacturing’ (RDM), which is a major focus of current industrial policymaking, in the UK as elsewhere. A range of different possible organisational models for 3D bioprinting can be envisioned. These range from ‘surgeon-led’ to ‘automated’ processing models, with a second range of more or less centralised, distributed or third-party producers located in hospitals or other centres. As many laws were not made with decentralised and additive manufacturing in mind, these models each entail different regulatory and liability scenarios. The purpose of the paper is thus to survey the regulatory landscape in relation to RDM in 3D bioprinting, looking for gaps, problems, and uncertainties in the uptake of this technology. We explore the potential legal implications of the footprint of bioprinting in correspondence with its possible RDM product configurations. We consider a provisional ‘process-based’ approach to responsive co-regulation and assess the two governance pillars of regulation and product liability in the UK and European Union context. The discussion aims to identify the future regulatory directions for better facilitating bioprinting and bioprinter technologies to best fit within current regulations.

The following section will introduce the state of the art of RDM in 3D bioprinting. Our analysis identifies apparent ‘gaps’ and interpretational uncertainties in both *ex ante* and *ex post* dimensions of existing regulation. Section 3 examines the *ex ante* dimensions of regulation, with a special focus on the relevant medical products and ATMP laws and regulations in the EU/UK, pointing out current gaps and contentious uncertainties especially of what we shall discuss as ‘mass customisation’. Section 4 then assesses the *ex post* aspects of regulation by exploring the elastic concepts of products, defects, and producers in the product liability regime, again identifying key uncertainties. We consider that a provisional ‘process-based’ approach

to co-regulation will be fit for purpose during the initial development phase of RDM bioprinting. We then conclude in Section 5 with remarks on future work.

2. Re-distributed manufacturing (RDM) in 3D bioprinting biofabrication

‘Biofabrication’ is a term used to describe production methods in tissue engineering and RM that could revolutionise healthcare delivery. It is a broad concept that encompasses several different types of manufacturing approaches to tissue engineering,⁷ which can be summarised as comprising two main process methods: 3D bioprinting and bioassembly.⁸ In this work, we examine the case of 3D bioprinting in RDM as a typical scenario reflecting the key issues in regulating biofabrication. We anticipate that the insights garnered from this work will be equally applicable to other areas of biofabrication.⁹

2.1 A novel manufacturing process

Three-dimensional printing is a technology that in principle enables ‘agile’ and responsive manufacturing to take place at locations closer to the patient. 3D bioprinting refers to 3DP of biomaterials, such as human cells and tissues, typically constructed in a microstructural host called a ‘scaffold’, potentially providing an efficient solution to tissue engineering and regenerative medicine challenges where issues of scale-up and standardisation have been prominent. Bioprinting is thus a ‘processing method’ that can be used to handle human cells and tissue.¹⁰

⁷ Jürgen Groll et al. ‘Biofabrication: Reappraising the Definition of an Evolving Field’ (2016) *Biofabrication* 8, 013001.

⁸ *ibid.* 3D bioprinting refers to the direct spatial arrangement of cells and materials; bioassembly has a similar effect but uses automated assembly of cell containing building blocks.

⁹ See Section 4.3.

¹⁰ Daniel J Thomas, Zita M. Jessop, and Iain S Whitaker (eds) *3D Bioprinting for reconstructive Surgery: Techniques and Applications*, (Woodhead Publishing, 2018) Forword xv. Thomas, Jessop, and Whitaker note that: ‘3D bioprinting technology is currently being progressed as a method to engineer complex tissues and organs. This rapid growing technology allows for precise placement of multiple types of cells, biomaterials, and biomolecules in spatially predefined locations within 3D structures’.

The goal of bioprinting is to work with organic materials in order to create structures approximating body parts. Bioprinting will usually apply a patient's own cells ('autologous') to create a new therapeutic construct. The typical steps involved in using a bioprinter with autologous cells are: collect and grow cells from patient biopsies, make sufficient biological liquid ('bioink') combining cells and a hydrogel (polymer-based) containing medium to print tissues guided by software, mature the printed tissues before implantation. Bioprinting can be used to fill in a structural gap in a body part, or it can involve developing a scaffold into which living cells will be printed and then continue to grow.¹¹ Apart from direct therapeutic products, the application of such structures includes creating 'tissue-on-a-chip' for disease modelling or in vitro drug testing, and ultimately the potential of growing human organs.¹² Many experimental tissue-engineered clinical applications have been developed based on this method.¹³ At present, cell viability and vascularisation of printed tissues are the critical challenge to printing a functional organ.¹⁴

2.2 A novel distribution model

In terms of the uptake of bioprinting, we can distinguish broadly two organisational modes: centralised or Redistributed Manufacturing (RDM), each entailing different implications for regulation and legal liability.

In centralised bioprinting, patients would be diagnosed in dispersed hospitals, data scanned in hospitals and sent to the manufacturing site. Products are then manufactured at that

¹¹ Gordon G Wallace et al. *3D Bioprinting: Printing Parts for Bodies*, (ARC Centre of Excellence for Electromaterials Science (ARCS) Australia, 2014) 57.

¹² Niki Vermeulen and others '3D Bioprinting Me: a Socioethical View of Bioprinting Human Organs and Tissues' (2017) 43 *Journal of Medical Ethics* 618-624.

¹³ These include: 3D bioprinting bone, cartilage, breast reconstruction, nerve, skin, urinary bladder, trachea, and blood vessels. Thomas, Jessop, and Whitaker (n 10); Matthew Varkey and Anthony Atala 'Organ Bioprinting: A Closer Look at Ethics and Policies', (2015) 5(2) *Wake Forest Journal of Law & Policy* 275-298.

¹⁴ *ibid*, Varkey and Atala, at 294.

one central site, and then shipped back to hospitals.¹⁵ On the other hand, RDM of bioprinting refers to decentralised business models that place bioprinters in local hospitals or third party centres. Associated benefits in principle would include reduced product lead-time; no need to ship living cells; patient data retained within the hospital. However, there exist higher technical and regulatory hurdles for RDM bioprinting. The main issues to be considered will revolve around issues including quality control and timing of release of goods, regulatory compliance, process control and licensing, training and accountability, and the authority for release of goods.¹⁶ The fundamental question is in what ways we could expect local clinics to satisfy the regulatory requirements and quality control. We cannot expect regulatory monitoring and enforcement to be as intensive or as effective where we are dealing with localised bioprinting unless regulators are given large resources for this purpose.

In spite of the above technical and organisational hurdles to producing ATMP products, RDM of 3D bioprinting may offer a useful solution by providing customised therapy, reducing the distance to treatment, and locating accountability within the hospital. In terms of access to healthcare, it can also facilitate wide dissemination of this technology. Redistributed Manufacturing generally refers to ‘technologies, systems and strategies that change the economics and organisation of manufacturing, particularly in relation to location and scale’.¹⁷ The UK Government Office of Science states that ‘[T]he factory of the future may be at the bedside, in the home, in the field, in the office and on the battlefield’.¹⁸ The World Economic Forum in 2017 also predicts that ‘[Re]distributed manufacturing will disrupt traditional labour

¹⁵ EPSRC RiHN (Redistributed Manufacturing in Healthcare Network), 3D Bioprinting: Commercialising personalised ATMP/device combination products (Nottingham, RiHN 2015-16) <<http://rihn.org.uk/feasibility-studies/3d-bioprinting-feasibility-study/>> accessed 25 January 2019.

¹⁶ RiHN report, Cell Micro-factories: Feasibility of a Redistributed Manufacturing Model for Cell Based Therapies <<http://rihn.org.uk/wp-content/uploads/2015/10/Loughborough-Handout.pdf>> accessed 29 January 2019.

¹⁷ EPSRC Website, <www.epsrc.ac.uk/research/ourportfolio/themes/manufacturingthefuture/activities/rdmnetworks/> accessed 29 January 2019.

¹⁸ The UK Government Office for Science Foresight, The Future of Manufacturing: A New Era of Opportunity and Challenge for the UK (Project Report 2013).

markets and the economics of traditional manufacturing'.¹⁹ It is a business model that disperses the line of production in order to meet the demands for 'agile' manufacturing. Some form of RDM is likely to be the manufacturing approach for many production sectors, including personalised cell-and gene-based therapies.²⁰ It is advocated as an efficient way to reduce supply chain costs, improve sustainability, produce customised healthcare products, and promote equitable and more local access to health technologies. It is anticipated that with the RDM model, healthcare products could be prescribed, custom-designed, and manufactured on the basis of a single visit to a nearby clinic.

In commenting on RDM and 3DP used in healthcare, Mark Bale, the Deputy Director in Genomics Science & Emerging Therapies at the UK Department of Health, anticipated that

'Redistributed Manufacturing (RDM) in healthcare has the potential to transform the way in which medicines are supplied within the healthcare sector. It has the potential to make the system much more resilient and responsive and may lead to significant simplification of the supply chain. In addition, the use of additive manufacturing systems can completely transform how medicines are delivered to patients in terms of both new combinations and entirely new formats'.²¹

Following from the transformation in the manufacturing model in healthcare, he further argued that '[T]he way in which medicines are regulated will need to be fundamentally rethought'.²² It is suggested that setting the framework for a regulatory and governance pathway for RDM in healthcare is a policy priority.²³ The footprint and organisational model

¹⁹ World Economic Forum, Technology and Innovation for the Future of Production: Accelerating Value Creation (White Paper in collaboration with A.T. Kearney, 2017).

²⁰ Richard P Harrison, Qasim A Rafiq, and Nicholas Medcalf, 'Automated Decentralized Manufacturing of Cell & Gene Therapy Products' (2016) 2(4) *Cell Gene Therapy Insights* 489.

²¹ Redistributed Manufacturing in Healthcare Network (RIHN), Redistributed Manufacturing in Healthcare: Creating New Value through Disruptive Innovation (RIHN White Paper, 2017) 2. <http://rihn.org.uk/wp-content/uploads/2018/01/RiHN_WP_Full_double_web.pdf> accessed on 29 January 2019.

²² *ibid* 2.

²³ *ibid* 31.

of re-distributed applications will structure the public's accessibility to therapies derived from technologies including bioprinting. Yet, the feasibility of a RDM model of bioprinting will need to be assessed against the existing centralised one in terms of technical and regulatory hurdles. In terms of legal regulation, Vermeulen and colleagues suggest intellectual property (IP) rights, and product classification and market approval pathway as the major areas that need further clarification.²⁴ While we have considered the IP dimensions elsewhere,²⁵ this work is primarily focused on the role of co-regulation for governance, the classification and market approval pathway in *ex ante* regulation, and product liability and the duty to review in the *ex post* regulatory phase.

In the following section we investigate the *ex ante* aspects of the regulatory landscape for 3D bioprinting, of which the primary concern is checking the safety of 3D bioprinting before it and its products are licensed or authorised for use. We discuss whether a focus on 'process' regulation will be appropriate, and whether the current regenerative medicine regulations are fit for purpose for regulating bioprinting products.

3. The *ex ante* dimensions

From a manufacturing process perspective, ATMPs present intrinsic quality challenges, due to the novelty, complexity and technical specificity, which differ from those of medical devices and synthetic or non-living biological therapies.²⁶ As discussed above, it is anticipated that

²⁴ Vermeulen and others (n 12).

²⁵ Phoebe H Li, '3D Bioprinting Technologies: Patents, Innovation and Access' (2014) 6(2) *Law, Innovation and Technology* 147-169; Phoebe Li, '3D bioprinting: Regulation, innovation, and patents' in Daneil J Thomas, Zita M. Jessop and Iain S. Whitaker (eds) *3D Bioprinting for Reconstructive Surgery: Techniques and Applications* (Woodhead Publishing 2018) 217.

²⁶ The main hurdles to quality controls include: the starting materials have high variability and are scarce materials that only allow limited opportunity for sampling and testing; the materials and final products have a short shelf-life, restricting time for quality control tests, and, each manufacturing process may need to be individually adapted or tinkered (typically by a surgeon) due to changes in cell culture conditions or patient-specific factors such as anatomy. European Commission, Good Manufacturing Practice for ATMPs (Public Health Information) <http://ec.europa.eu/health/files/committee/75meeting/2c_2015_10_21_gmps_pharma_committee.pdf> accessed 29 January 2019.

RDM of 3D bioprinting would facilitate the viability of biomaterials and products by shortening the product cycle.

That said, we still need to attend to two types of risks associated with RDM bioprinting. The first type of risks is associated with the novel *additive* manufacturing processes and diffusing methods in the chain of custody, which may differ depending on the exact constitution of organisations involved and the relations between them. The second type of risks arise inherently from the quality of materials and products that is shared with other existing tissue engineering products. As 3D bioprinting is still a nascent way of building cells and tissues to be implanted into human body, the properties and associated risks remain unclear. Considering the novel production methods of additive manufacturing, a typical problem is whether a bioprinted scaffold and organ has less strength, stability and toughness that could lead to a higher probability of a ‘fracture’ and a defect after implantation. New medical treatment delivered via bioprinting will require a robust regulatory process for assessing the safety and effectiveness of therapy.

Crucially, one of the key governance questions is whether bioprinted products are to be differentiated from their counterparts made from conventional ‘subtractive’ production methods. In other words, whether bioprinting is to be deemed as a new classification in regulation due to its novel additive manufacturing process. We expand on this below.

3.1 Process/product- based regulation

Arguments for *prudential* regulatory judgments about health and safety have long been raised on potential regulatory shifts adapted to Products introduced by novel Production Methods (PPMs) that entail uncertain risks to human health and the environment.²⁷ Examples such as

²⁷ The PPMs debates arise primarily from the WTO Agreement on Technical Barriers to Trade (TBT Agreement). See: Peter Van den Bossche and Werner Zdouc, *The Law and Policy of the World Trade Organization: Text, Cases and Materials* (4th edn, Cambridge University Press, 2017) 887.

genetically modified organisms (GMOs) and nanotechnology could offer some precedence for bioprinting governance as both of their regulatory profiles follow a similar vein – whether a ‘process-based’ regulatory regime would be appropriate for managing uncertain risks associated with conventional products delivered via *novel production methods*. In other words, in terms of prudential regulation, whether existing products manufactured by novel production methods should be categorised differently from their conventional equivalents in the regulatory landscape. This approach is indicated by the common statement in regenerative medicine that ‘the product is the process’.

We suggest that the core theme of 3D bioprinting governance lies upon repetitive debates on ‘product/process-based’ approach to regulation. We argue that, at the technological development phase when information and scientific evidence are still lacking, a ‘process-based’ approach is a prudential regulatory judgment that focuses on the protection of health and safety. It is unwise to turn a blind eye on the potential adverse effects arising from various novel manufacturing ‘processes’ in making a product. Taking the action of discerning and distinguishing the risks arising from new process methods would then seem both prudent and ethical.

Approaches to regulating GMOs vary from different jurisdictions. While GMOs attract tenacious social and political resistance in the EU/UK, a precautionary framework has been adopted that follows a ‘process-based’ regulatory regime; yet in North America, a more permissive ‘product-based’ regime that treats GMOs products as equivalent to conventional products has developed. Maria Lee sketched a clear picture of how the EU struggles to harness the tension between managing scientific risks and societal values at the EU and national planes in the regulation of cultivating GMOs.²⁸ In some particular scenarios, based upon the

²⁸ Maria Lee, ‘GMOs in the Internal Market: New Legislation on National Flexibility’ (2016) 79(2) *Modern Law Review* 317.

precautionary approach, provisional measures targeted to protection of health and the environment may be triggered in the EU.²⁹ It is to be clarified the extent to which a more stringent ‘process’ approach as opposed to the ‘product’ approach will still be justifiable under the ‘free movement of goods’ principle in free trade.

Similarly, at the core of debates revolving around regulating nanomedicine, the novel nanoscale production of nanoparticles also entails uncertain risks to health and the environment. Nanomedicine can contribute to customised personalised medicine via the controlled release system that increases the effectiveness of a drug (or device) by the bioactivity of the surface of nanoparticles.³⁰ It is unclear that whether the risk profile of a medicinal product produced via nanotechnology would be deemed equivalent to conventional products. Dorbeck-Jung and Chowdhury suggest that it may not be appropriate to apply a ‘stricter’ regime to cope with the classification problems of combined products, yet there is a case for nanomedicine to be licenced through the centralised medicines authorisation process in the EU, as opposed to the relatively relaxed devolved approach of private authorisation bodies (‘notified bodies’) and private standards that applies to medical devices.³¹

The GMOs and nanomedicine cases illustrate the importance of issues of the boundary between products and production processes in novel high-tech biotechnology innovations. Similarly, RDM in bioprinting entails its own challenges to the current governance system, particularly in two areas: regenerative medicine regulations and the product liability regime. In the following section, we evaluate the applicability of bioprinting technologies in the EU medical device and ATMPs and RM product regulations, noting where existing provisions currently appear applicable and possible lacunae and areas of ambiguity or lack of clarity.

²⁹ *ibid.* Here we use ‘precautionary approach’ instead of ‘precautionary principle’ to denote the adaptability and flexibility of moderate risk management.

³⁰ Bärbel R. Dorbeck-Jung and Nupur Chowdhury, ‘Is the European Medical Products Authorisation Regulation Equipped to Cope with the Challenges of Nanomedicines?’ (2011) 33(2) *Law & Policy* 276 at 294-5.

³¹ *ibid.*

3.2 Existing regenerative medicine product regulation

A key question regarding the relevant regulatory frameworks already in existence is whether there is anything novel about bioprinted *products* as material artefacts that may not be already provided for in the legislation and related implementing guidance and interpretations. Possibly the main novelty is the repeated production of individualised products, using the same bioprinting equipment, which is a *process* issue. The characteristics of the process will always be the same. Producers (however defined)³² will need guidance on the question: Is this process going to be subject to a tranche of legislation that relates to customised, distributed manufacture, or will it fall under the practice of medicine? Our initial view is that the main novelty lies in the *processes* of manufacture, rather than in the product itself, as the process introduces the potential for unwanted variability in addition to the customisation. It is nevertheless important to review the place that bioprinted RM products are likely to have in the existing medical product regimes. Here we note that not only that there is a recurrent question about process and product in the existing regenerative medicine product regulation, but also that much of the interpretive uncertainty arises because the regulatory regimes were not articulated with distributed bespoke (customised) manufacture in mind.

ATMPs rely for their efficacy on cellular or genetic primary modes of action and, as such, are currently regulated as a special class of ‘medicinal products’ in the EU. The nature of a bioprinted product is that it has the characteristics of an ATMP and some similarity to an ATMP-device combination product. Most bioprinted therapeutic products will be ‘combined’ products or ‘combination products’. This refers to a unique production method involving ‘co-printing’ of cells and scaffolds, as outlined above. Depending upon the characteristics and primary mode of action of the products, different existing product regimes will be applicable.

³² We discuss the definition of ‘producer’ in Section 4.2.2.

Therefore, although the current regulatory difficulties relate to the issues of specification, it would at least have to be approved by the route of a medicinal product and as an ATMP. Due to the limit of the work, we will focus only on the four main regulatory regimes, leaving aside any potential secondary issues.³³

3.2.1. Relevant primary legislations

These are four main regulatory regimes covering regenerative medicine products applicable currently in the UK, each being covered by a set of EU legislation: tissues and cells, medical devices, pharmaceuticals, and ATMPs. The EU ‘Tissues and Cells’ Directive covers a range of processes from sourcing of human material to storage and processes such as cleaning etc.³⁴ This Directive is applicable to the human biomaterials that would be used in a bioprinted product, in the same way as a product created by other laboratory methods. The latter is administered in the UK by the Human Tissue Authority, and the former three areas by the Medicines and Healthcare products Regulatory Agency (MHRA). The UK regulator the MHRA implements relevant regulations in the UK, and makes notable interpretations of flexible provisions (such as the ATMP Hospital Exemption).

The regulations for pharmaceuticals, medical devices and ATMPs are designed, with certain important exemptions, to cover commodities which can be placed on the market. Medical devices and medicinal products are regulated in two different instruments: the new Medical Device Regulation 2017/745 concerns medical devices (MDR);³⁵ while Directive

³³ See also: Phoebe Li and Alex Faulkner, ‘3D Bioprinting Regulations: A UK/EU Perspective’ (2017) 8(2) *European Journal of Risk Regulation* 441-447. Secondary issues include the Machinery Directive, HFEA, the Orphan Medicinal Product Directive, GMOs Regulations, ISO Standards, GMP/GCP; Blood Directive, General Data Protection Regulation, Biotech Directive, Clinical Trial Directive, Guideline Good Distribution Practice, Product Liability Directive, Falsified Medicines Directive, REACH, Synthetic Biology, Nanomedicine/material Regulation, Digital Society; IT/eHealth.

³⁴ Council Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells OJ L 102.

³⁵ Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices,

2001/83/EC deals with medicinal products for human use.³⁶ For the purposes of this discussion, it is important to note that the definition of medical device includes both implants and (therapeutically significant) software. If the medical device and the medicinal product constitute a single integrated unit, which is to be used exclusively in a given combination and not reusable, then the product will fall under Directive 2001/83.³⁷

While bioprinted therapeutic products will not be pharmaceuticals in the conventional sense, the ATMPs Regulation 2007 is a *lex specialis* to the Medicinal Products Directive that specifically deals with nascent ‘advanced therapies’ (a unique designation invented for the purposes of classifying these emerging technologies), comprising gene therapy, somatic cell therapy, tissue engineered products, and combination products (e.g. a cell therapy – medical device combination).³⁸ Combination products comprising of viable cells and tissues together with a medical device component will automatically fall under the ATMPs Regulation.³⁹ In other words, the ATMPs Regulation is the major regulatory instrument qualifying most, though not all, RM products in the EU, and it is part of the pharmaceutical product regime. It is administered by the central EC ‘Committee for Advanced Therapies’ (CAT), comprising a

amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC OJ L 117 (Medical Device Regulation, MDR), art 2. ‘Medical device’ is defined as: ‘any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings’ for one or more medical purposes.

³⁶ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use OJ L 311 (Medicinal Product Directive), art 1(2) & (3).

‘Medicinal product’ means ‘any substance or combination of substances presented for treating or preventing disease in human beings. Any substances or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product’. Substance comprising a medicinal product may include ‘any matter irrespective of origin which may be human’.

³⁷ Council Directive 93/42/EEC of 14 June 1993 concerning medical devices OJ L 169, Art 1 (3).

³⁸ Council Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 OJ L 324 (ATMPs Regulation); for its history see A Faulkner ‘Tissue engineered technologies: regulatory pharmaceuticalisation in the European Union’ (2012) 25 *INNOVATION: the European Journal of Social Science Research*, 4, 389-408.

³⁹ ATMPs Regulation, Recital (4).

range of appropriate technical expertise (including medical device should such a component be present in a given product).

We can see that a bioprinted product will be either a ‘cell therapy medicinal product’ or more likely a ‘tissue engineered product’ (TEP), or either of these ‘combined’ with a medical device component.⁴⁰ Due to the additive manufacturing process of building cells or tissue layer-by-layer which involves structural changes and manipulations, most 3D bioprinted products would be considered tissue engineered products.⁴¹ Cells and tissues are considered ‘engineered’ (i.e. not a simple graft or transplant) if they have been subject to ‘substantial manipulation’ with a view to achieving novel biological, physiological or structural properties.⁴² If cells have *not* been ‘substantially manipulated’ and/or do not perform a function in the body different to their original function (non-homologous), the product will be regulated as a *transplant*.⁴³ It appears conceivable that some bioprintable therapies using autologous cells of a certain type that have merely been derived from a multiple cell/tissue source without enrichment or manipulation etc. could be deemed to be *transplants*, thus avoiding ATMP, device or pharmaceutical regulatory requirements.

The MDR and ATMPs Regulation are mutually exclusive.⁴⁴ But both should be applicable in the case of combination products which comprise both medical device and a medicinal substance, including a human blood or plasma derivative, or tissues or cells of human origin (Reg 722/2012). Such a combination product could conceivably be 3D-printed, though it would not be considered *bio*-printed.

⁴⁰ These are designations that the European Medicines Agency’s Committee for Advanced Therapies adjudicates on. In the case of a medical device component, the above discussion on customised aspects will apply.

⁴¹ Annex I ATMPs Regulation sets out the criteria of not fulfilling ‘substantial manipulation’, including: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation, and vitrification.

⁴² ATMPs Regulation, art 2 (C).

⁴³ Paul C Hourd, ‘A 3D Bioprinting Exemplar of the Consequences of the Regulatory Requirements on Customised Processes’ (2015) 10 (7) *Regenerative Medicine* 863.

⁴⁴ art 1(6) (g); art 1 (13).

3.2.2 Do we need a new bespoke regulatory regime for ‘mass customisation’?

Following from the above discussions, the question is highlighted whether cell- and tissue-based therapeutic products made via novel applications of additive manufacturing could fit under the existing legal framework or, rather, merit a distinct separate regime to regulating uncertain risks deriving from the production method. In other words, we have to ascertain if bioprinting governance would merit a ‘product’, ‘process’, or ‘process/product’ -based regulation regime: whether a 3D bioprinted organ or tissue could be deemed ‘equivalent’ to traditional transplants and ATMPs, or should it be governed under a bespoke and distinctive regime, due to the novel production process of 3D printing? And in the case of the ATMPs Regulation and the UK ‘Specials’ license, how far do these measures take account of novel production methods? Our initial view is that since there are built-in flexibilities in place, we may take the position to wait and see how the flexibilities evolve within the current regime before making any change to the existing framework.

Apart from the novel production method, the defining characteristic of bioprinting regarding the product is that it might allow a degree of ‘personalisation’ or ‘customisation’ of constructs to an individual patient that has not been envisioned previously. The tension, from a regulatory point of view, between an arguably standardised method of production and a customised product (‘mass customisation’) is the source of the main uncertainties surrounding bioprinted products. Both the medical device and the ATMPs regimes have provisions in the form of regulatory exemptions for customised ‘one-off’ products for individual patients. We discuss these here.

In 2017, a new revision of EU medical device regulations came into force, and like the former three medical devices directives, this allows for ‘custom-made’ medical devices.⁴⁵ This

⁴⁵ Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active

category appears to include bioprinted products that have regenerative function, such as ‘bioactive’ personalised hip or knee implants. Expert commentator Vollebregt has pointed out that the Explanatory Memorandum to the new Medical Device Regulation states that ‘Manufacturers of medical devices for an individual patient, so called “custom-made devices”, must ensure that their devices are safe and perform as intended, but their regulatory burden remains low’, but designation of bioprinted implants as low-risk is questionable. He further points out: ‘the only safeguards are the manufacturer’s diligence, the prescription that defines the custom made device and the ex-post controls (i.e. post-marketing surveillance, vigilance systems, and data collection) exercised by competent authorities (i.e. national medical device regulatory agencies)’.⁴⁶

The MDR exempts health institutions from certain responsibilities when it comes to a need to manufacture, modify or use medical devices, on a non-industrial scale, for special needs of target patient groups.⁴⁷ Specifically, it clarifies that ‘custom-made’ devices do not include ‘mass-produced devices which need to be adapted to meet the specific requirements of any professional users and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices’.⁴⁸ 3D bioprinted products, appear to fall beyond the

implantable medical devices (90/385/EEC) OJ L 189; Council Directive 93/42/EEC of 14 June 1993 concerning medical devices OJ L 169; Council Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices OJ L 331. See also: Charlotte Ryckman, ‘First European Commission Borderline Decision: Does it Answer or Raise Questions?’ (*Inside Medical Devices*, 20 May 2016) <www.insidemedicaldevices.com/2016/05/first-european-commission-borderline-decision-does-it-answer-or-raise-questions/> accessed 29 January 2019; Wim Vandenberghe, ‘New EU Rules for Medical Devices’ (*Medical Devices*, 12 July 2016) <www.sheppardhealthlaw.com/2016/07/articles/medical-devices/new-eu-rules-for-medical-devices/> accessed 23 January 2019; Erik Vollebregt, ‘The Final Text of the IVDR: First Impressions’ (*Medical Devices Legal*, 30 June 2016) <<https://medicaldeviceslegal.com/2016/06/30/the-final-text-of-the-ivdr-first-impressions/>> accessed 29 January 2019.

⁴⁶ Erik Vollebregt, ‘3D Printing of Custom Medical Devices under Future EU Law’ (*Medical Devices Legal*, 05 March 2014) <<https://medicaldeviceslegal.com/2014/03/05/3d-printing-of-custom-medical-devices-under-future-eu-law/>> accessed 29 January 2019.

⁴⁷ MDR Recital 30. Health institutions including hospitals, laboratories and public health institutions that support the healthcare system and/or address patient needs, but which do not treat or care for patients directly.

⁴⁸ MDR art 2(3).

scope of ‘custom-made’ device in the MDR as they are arguably ‘mass-produced devices’ that need to be adapted within a pre-defined range by means of industrial manufacturing processes in accordance with the written prescriptions of an authorised person. The MDR also clarifies that software with a medical function is deemed to be an ‘active’ device.⁴⁹ This means that increasingly stringent active device regulations would be applicable to software that converts MRI or CT scanning images into digital data files for guiding a bioprinter.

The ATMPs Regulation was formally reviewed in 2013,⁵⁰ and several areas of controversy that might impinge on bioprinted medical products were identified. The most controversial aspect was the so-called ‘hospital exemption’ and its definition of ‘routine’ versus ‘non-routine’ and ‘industrial’ versus ‘nonindustrial’ production, clearly impinging on the issue of mass customisation that bioprinting raises. To qualify under hospital exemption, a product should meet all of the following criteria: preparation on a non-routine basis; preparation according to specific quality standards (equivalent to those for ATMPs with a centralised marketing authorisation); use within the same Member State; use in a single hospital; use under the exclusive responsibility of a medical practitioner, and compliance with an individual medical prescription for a custom-made product for an individual patient. The main concern has been that while this measure might support clinical innovation, it may also be seen as anti-market, or in other words, a backdoor for producers to get their product adopted.⁵¹

⁴⁹ Regulation 2017/475, art 2(4). An active device means ‘any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy’.

⁵⁰ 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 [2014] COM(2014) 188 final; Commission, Regulation (EC) No. 1394/2007 on advanced therapy medicinal products: summary of the responses to the public consultation [2013] SANCO/D5/RSR/iv(2013)ddg1.d5.

⁵¹ See K Alheit, ‘The Applicability of the EU Product Liability Directive to Software’ (2001) 34(2) *The Comparative and International Law Journal of Southern Africa* 188-209; MHRA, ‘Guidance on Legislation: Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC’ (MHRA: London, 2013); Erik Vollebregt, ‘More on 3D Printing (and Biofabrication)’ (*Medical Devices Legal*, 17 July 2014) <<https://medicaldeviceslegal.com/2014/07/17/more-on-3d-printing-and-biofabrication/>> accessed 29 January 2019.

It is known that few products have been authorised by MHRA in the UK under this ATMP exemption to date, whereas the so-called ‘Specials’ medicinal products exemption is more widely used, the reason possibly being that unlike the HE, the Specials route allows import and export of biomaterials (MHRA, personal communication). The definition of routine/non-routine and ‘industrial’ production is crucial to the regulation of bioprinted products under the current regimes. In the UK, the MHRA states that it monitors repeated production of the ‘same’ products for individual patients.⁵² Hence, a main area of regulation to be resolved is whether bioprinted products, repeatedly using the same manufacturing equipment, will be regarded as operating in a routine/industrial, or nonroutine/craft-like manner. At face value, the typical bioprinting process is not quite the same as the production process envisaged or implied in ‘Specials’ or the ATMP Regulation hospital exemption or medical device in-house exemption. From the medical device perspective, Vollebregt suggests:

‘[Y]ou could also argue that 3D printing is customisation of a standard virtual device defined in a software model rather than custom production according to a production process that is not already fully determined in advance, which would be the case for a true traditional custom-made device’.⁵³

This key issue thus remains ambiguous.

We can see that the existing regulatory regimes are ‘product-’ based and thus little attention is paid to the unique implications of novel processes. Overall, the current regulatory regimes do not afford sufficient margin for addressing the impacts brought by RDM. Similarly, the current ATMPs and Medical Device regimes do not directly engage with the novel bioprinting processes, except broadly for some routes for exemptions and Specials, in which

⁵² MHRA, Guidance on ‘non routine’

<www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf> accessed 23 January 2019.

⁵³ Erik Vollebregt, ‘3D Printing of Custom Medical Devices under Future EU Law’ (*Medical Devices Legal*, 05 March 2014) <<https://medicaldeviceslegal.com/2014/03/05/3d-printing-of-custom-medical-devices-under-future-eu-law/>> accessed 23 January 2019.

manufacturing processes have been considered in terms of standardisation and/or customisation.

In summary, the current EU ATMPs Regulation is the legislative instrument that will be most applicable to bioprinted therapeutic products produced at UK facilities (and similar provisions are likely to continue if and when the UK leaves the EU). Crucially, there remain regulatory uncertainties as to how ‘mass-customised’ products can, and should be classified and regulated. Such uncertainties are exacerbated when one takes into account the wide range of potential organisational models for implementing bioprinting services, whether that be centralised or variously ‘redistributed’ and reconfigured. Such concerns are key to issues of accountability. Since the technology as well as the legal landscape is still adapting within the extant flexibilities, it may be too early to conclude if the above exemptions are not fit for purpose and that a new and bespoke regime would be desirable. Nevertheless, we do see a need to adopt a provisional ‘process-based’ approach, which we will expand on below. We also consider how a co-regulation approach would facilitate governance and interpretation of the legal uncertainties associated with 3D bioprinting.

3.3 A provisional process-based approach

New emerging technologies usually engender suspicions and uncertainty due to insufficient knowledge about their likely development. Too often we can see products are raced to market, and then experiencing several ‘boom and bust’ cycles before consumers and regulators accumulate sufficient knowledge and trust in them. As Brownsword and Goodwin describe:

‘Where technologies are in an emergent state, the knowledge base will tend to be low; in particular, without any experience of use, the longer-term consequences will be unknown. Moreover, where technologies, such as nanotechnologies and synthetic biology, are characterised by their novel properties, uncertainty is almost an immanent

virtue. In these circumstances, there will be a lack of scientific consensus to guide the regulator. How should regulators proceed in such conditions of low knowledge and low consensus?’⁵⁴

In response to the acceleration of new emerging technologies, there will be a need for ‘regulatory phasing’ that would respond to regulatory priorities at various points of technological development. Regulatory phasing also corresponds to the rationale of ‘processual regulation’,⁵⁵ where a temporal-spatial examination of regulatory spaces and practices could be tempered by stakeholders. Brownsword notes that the first phase regulation focus on controlling, confining and channeling *ex ante* the particular aspect of practice that is its target, while the second phase regulation operates *ex post*, endeavouring to compensate for, or in response to, the consequence of a practice that cannot be controlled in the first phase.⁵⁶ Various models of technology regulation across a wide spectrum have been deliberated, ranging from absolute prohibition to no specific regulation.⁵⁷ It may be unsatisfactory to just rely on ‘inherited regulation’ that confines the life-cycle of an emerging technology within existing regimes. Equally, advocates for a precautionary approach have contested the ‘evidence- and risk-based’ reactive model that failed to embed non-scientific factors into deliberation. An incremental, piecemeal, or ‘muddling through’ approach to regulating nanotechnologies has received criticisms due to the lack of a coherent regulatory governance system.⁵⁸

The emergence of distributed innovation again poses new challenges to the regulatory regime as these practices often lie outside the ambit of law and regulation. Lin describes that

⁵⁴ Roger Brownsword and Morag Goodwin, *Law and the Technologies of the Twenty-First Century: Text and Materials*, (Cambridge University Press, 2012) 129.

⁵⁵ Samuel Taylor-Alexander and others, ‘Beyond Regulatory Compression: Confronting the Liminal Spaces of Health Research Regulation’ (2016) 8(2) *Law, Innovation, and Technology* 149-176.

⁵⁶ Roger Brownsword, ‘Red lights and rouges: regulating human genetics’ in Han Somsen (ed) *The Regulatory Challenge of Biotechnology: Human Genetics, Food and Patents* (Edward Elgar, 2007) 41.

⁵⁷ Bärbel Dorbeck-Jung and Diana M. Bowman, ‘Regulatory Governance Approaches for Emerging Technologies’ in Diana M. Bowman, Elen Stokes, Arie Rip (eds) *Embedding New Technologies into Society: A Regulatory, Ethical and Societal Perspective* (Pan Stanford Publishing, 2017) 35-59.

⁵⁸ *ibid* 40-42.

‘[D]istributed innovation involves extremely rapid change, unpredictable systems, and highly uncertain effects’.⁵⁹ Accordingly, he proposes a paradigm consisting three general approaches for governance: a ‘Big Data/Big Government’ approach, an approach relying on nongovernmental intermediaries’ oversight, and a self-regulatory approach.⁶⁰ As each approach has inherent strengths and limitations, he subsequently suggests that a context-specific analysis should be conducted before choosing a particular course, and an *adaptive* model based on the three basic approaches will be moderated in the governance of different fields of distributed innovation.

Alternative regulatory models include responsive regulation, co-regulation, reflexive regulation, experimental regulation, and meta-regulation. Particularly, Brownsword and Somsen propose a ‘co-regulation’ approach, by which technological innovation operates with a ‘social license’, reflecting a shared responsibility of public and private regulators.⁶¹ It develops by empowering communications amongst stakeholders as collaborators including regulators, producers, users, and the society, which aims to overcome the limitations of a traditional one-way top down, or bottom up regulation. Likewise, Dorbeck-Jung and Bowman also contend that a responsive co-regulatory approach, striking an appropriate balance or combination of legislation and soft regulation should be developed, with a view to adapting to changing insights on new emerging technologies.⁶²

Due to the lack of knowledge at the initial development of an emerging technology, transparent, continuous and real-time communication between multiple stakeholders such as scientists, regulators, and consumers, before a product cycle is mature and proved safe, is, therefore, of paramount importance. This is where ‘co-regulation’ can be brought into

⁵⁹ Albert C. Lin, ‘Herding cats: governing distributed innovation’ (2018) 96(4) *North Carolina Law Review* 945.

⁶⁰ *ibid.*

⁶¹ Roger Brownsword and Han Somsen, ‘Law, Innovation and Technology: Before we fast Forward – a Forum for Debate’ (2009) 1 *Law, Innovation and Technology* 1-73.

⁶² Dorbeck-Jung and Bowman (n 60) 53.

consideration. Before then, regulators may need to take *provisional* measures to keep an adaptive approach to governance,⁶³ in order to meet the changing faces of risks associated with a new technology. This is why we propose a provisional ‘process-based’ approach to bioprinting governance. It is fair to say that a processual ‘process-based’ approach could be deemed as a *provisional* measure based on the precautionary approach, serving as a safety valve before the uptake of bioprinting technology has matured and its risk profile complete. It appears appropriate to initially take the ‘process-based’ regime, and then at a later regulatory phase to transit back to a ‘product-based’ regime, once the latest scientific review reveals that the uncertain risks have been identified and sufficiently addressed.

Discussions on the possible adaptation from a process- to a product- based approach to regulation could be found in the recent debates on regulating genome editing technologies. As opposed to the widespread concerns on GMOs, at a micro level, such as genome editing and the CRISPR/Cas9 technology, scientists argue that recent new methods of genetic medication are closer to conventional breeding than common genetic engineering. Conflicting views are that products of new breeding techniques that do not contain foreign DNA will fall beyond or within the current EU GMOs legislation.⁶⁴ It is contestable, in this context, whether a ‘process-based’ approach will need to adapt to a ‘product-based’ approach that would consider the novelty and risks of the specific product trait, as opposed to the process by which that trait was produced.⁶⁵ Nevertheless, the European Court of Justice (ECJ) decided in 2018 that organisms obtained by the new techniques of direct mutagenesis are GMOs and hence falls under the EU

⁶³ Roger Brownsword and Morag Goodwin (n 57) 132.

⁶⁴ Thorben Sprink and others, ‘Regulatory Hurdles for Genome Editing: Process- vs, Product-based Approaches in Different Regulatory Contexts’ (2016) 35 *Plant Cell Rep* 1493-1506; ‘Gene Editing in Legal Limbo in Europe - The European Union is Dragging its Feet on Gene-editing Rules and Scientists Should Push the Issue’ *Nature* (22 February 2017) <www.nature.com/news/gene-editing-in-legal-limbo-in-europe-1.21515> accessed on 7 January 2019. European Academies Science Advisory Council (easac), New Breeding Techniques (2015) <https://easac.eu/fileadmin/PDF_s/reports_statements/Planting_the_Future/New_breeding_techniques_-_EASAC_statement_July12.pdf> accessed 8 January 2019.

⁶⁵ Gary E Marchant and Yvonne A Stevens, ‘A New Window of Opportunity to Reject Process-based Biotechnology Regulation’ (2015) 6 *GM Crops & Food* 233-242.

GMO Directive.⁶⁶

Also recently, ‘Responsible Research and Innovation’ (RRI) has been proposed in debate about innovation governance, with a view to shifting the focus from risk regulation to a societally mandated support of beneficial innovation.⁶⁷ In this vein of seeking to balance risks and benefits, Vermeulen and colleagues consider a RRI model to be a proactive way to reflect interdisciplinary ethics for regulating bioprinting.⁶⁸ In addition, Vijayavenkataraman and colleagues set out a NEST-Ethics (Ethics of New and Emerging Science and Technology) model for bioprinting. Considerations include: sources and donation of cells, use of stem cells, ownership of printed tissue/organ, and ethics related to clinical translation.⁶⁹

Given the brief review of approaches outlined above, we anticipate that a responsible approach to regulating 3D bioprinting would be based on some form of multi-stakeholder ‘co-regulation’ to work toward social acceptance, and that the RRI model can be developed to engage various stakeholders with a view to balancing rights and responsibilities at the crucial phase of technological development. In a community of rights, the responsive co-regulation model will facilitate the respective roles of Big Data/Big Government, nongovernmental intermediaries, and industries to reconfigure themselves for the search of an optimal form of governance.

4. The *ex post* dimensions

In this section we continue to investigate the above queries in the regulatory landscape, turning to the *ex post* dimension, which is concerned with the matters of liability once bioprinting has

⁶⁶ *Confédération paysanne and Others v Premier ministre and Ministre de l’Agriculture, de l’Agroalimentaire et de la Forêt*, Case C-528/16, EU:C:2018:583 (ECJ (Grand Chamber)), 25 July 2018. Mutagenesis is a set of techniques that alters the genome of a living species with the insertion of foreign DNA.

⁶⁷ Dorbeck-Jung and Bowman (n 60) 39-40.

⁶⁸ Vermeulen and others (n 12).

⁶⁹ S. Vijayavenkataraman, W.F. Lu, and J.Y.H. Fuh (2016) ‘3D Bioprinting – An Ethical, Legal and Social Aspects (ELSA) Framework’, *Bioprinting* 1-2: 11-21.

been licensed or authorised for use. We will discuss relevant liability issues associated with bioprinted products, which arise alongside and have impact upon the regulatory uncertainties discussed immediately above.

4.1 The duty to review

The responsive co-regulation model applies to both *ex ante* and *ex post* regulatory phases, as it provides a constant engaging platform for facilitating the point for the possible transition of the process/product approach. In Brownsword's regulatory matrix, he considers a community of rights as 'a society that views itself as a process rather than a finished product', and thus it is a community that 'constantly keeps under review the question of whether the current interpretation of its commitments is the best interpretation'.⁷⁰ A 'co-regulation' approach would be beneficial in improving data gathering and sharing for review, filling newly created or exposed regulatory gaps, incentivising strong corporate stewardship, enhancing agency expertise and coordination, providing for regulatory adaptability and flexibility, and achieving substantial, diverse stakeholder involvement.⁷¹

Similarly, under international law, the provisional 'process-based' approach would need to be reviewed from time to time against the latest scientific evidence. Examples of imposing the mandatory duty to review after a provisional precautionary measure is adopted are evident in the International Court of Justice,⁷² the World Health Organization,⁷³ the United Nations Food and Agriculture Organization (FAO)/WHO Codex,⁷⁴ the Cartagena Protocol on

⁷⁰ Roger Brownsword, 'Nanoethics: old wine, new bottles?' (2009) 32 *European Journal of Consumer Policy* 355-379.

⁷¹ Dorbeck-Jung and Bowman (n 60) 40.

⁷² *Gabcikovo – Nagymaros Case* (1997) ICJ Report 7, paras 105-114.

⁷³ Revision of the International Health Regulations, Fifty-eight World Health Assembly, 2005, art 43.2.

⁷⁴ Codex Alimentarius Commission Procedural Manual 21st Edition (Codex Manual), p. 27
<<http://www.fao.org/3/a-i3243e.pdf>> accessed 23 January 2019.

Biosafety,⁷⁵ and the World Trade Organization.⁷⁶ More recently, considering the uncertain risks associated with heritable genome editing, the Nuffield Council on Bioethics strongly suggests that before any move is made to amend legislation (to allow heritable genome editing), monitoring and review mechanisms should be put in place.⁷⁷ It also stresses that a broad and inclusive societal debate will be required in assessing risks and the vulnerability to adverse effects.⁷⁸ A deliberate decision on whether, when, and how to transit the ‘process-based’ approach to a ‘product-based’ one would ultimately rely on new scientific revelations and public debate.

The post-market surveillance mechanism will feed back relevant data for assessing the provisional process regulation. Specifically, the ATMPs Regulation carries with it a requirement for 30-year traceability and discretionary risk management plans.⁷⁹ Traceability systems should be compatible with those defined in the Tissues and Cells Directive (2004/23/EC)⁸⁰ and when relevant the Blood Directive (2002/98/EC)⁸¹. The systems should ensure traceability of tissues, cells and derived ATMPs from the donor to the patient, and is also required for starting materials or precursors or any materials of human origin used in the manufacture of the ATMP. Pharmacovigilance measures for hospital-exempt ATMPs will be required, for example producers:

‘[s]hould ensure appropriate recording and reporting of suspected adverse reactions and events, in the context of the relevant legislative requirements for medicinal products,

⁷⁵ Cartagena Protocol on Biosafety, art 12.

⁷⁶ Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), Marrakesh Agreement Establishing the World Trade Organization, Annex 1A: Multilateral Agreements on Trade in Goods, art 5.7.

⁷⁷ Nuffield Council on Bioethics, Gene editing and human reproduction: social and ethical issues short guide, (2018), para 5.21.

⁷⁸ *ibid.*

⁷⁹ ATMPs Regulation, art 14(4).

⁸⁰ Council Directive 2004/23/EC.

⁸¹ Council Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC OJ L 33.

tissues and cells, or blood as applicable. In addition, any need for a risk management plan will be considered on a case-by-case basis'.⁸²

The data from such requirements should be analysed in regulatory review procedures.

In the case of regulating nanocosmetics, in 2009 the European Parliament and Council differentiated cosmetic products containing nanomaterials from those containing conventional particles in the context of the Cosmetic Regulation.⁸³ For the purpose of the Regulation, it developed a 'narrow' definition of nanomaterials to be within 1-100 nm size range. The narrow definition is deemed to likely undermine the effectiveness of the regulatory regime, but the Regulation also recognised that the definition may need to be updated in line with the evolving state of the scientific art (Recital 29). It also set out associated notification and labelling requirements for the products, with a view to promoting transparency and communication between industry and the consumer, and the market.⁸⁴ We see that such considerations of definition and transparency equally arise in the case of 3D bioprinting.

Considering these important but unresolved boundary issues, the *ex post* product liability regime seems to deal with some limited process issues, where 'products' and their 'producers' can be identified in the chain of custody. In the following section, we explore the possibilities of pursuing product liability claims following patients receiving treatment via 3D bioprinting.

4.2 Product liability

We explain above that risks and liability associated with bioprinting arise from two areas: first, those occurring primarily from the novel *additive* manufacturing and the RDM processes, and

⁸² HPRA, Guide to hospital-based Advanced Therapy Medicinal Products (HPRA: Dublin, 2013).

⁸³ Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products OJ L 342.

⁸⁴ Dorbeck-Jung and Bowman (n 60) 48-52.

second, those due to the specific properties of the bioprinted product per se.⁸⁵ Due to the involvement of different stakeholders such as Computer-Aided Manufacturing (CAM) designers and medical clinicians, decentralised CAM in the production chain further compounds the thorny issues of risk management in the ‘chain of custody’ and the ‘quality of materials’ of bioprinting and its products.

Available remedies for the users of defective products include the common law of contract and tort, and the UK Consumer Protection Act (CPA) 1987. *Ex post* liability for innovative but defective 3D bioprinting products is unlikely to be adequately covered by either the common law of contract as there needs to be a contractual relationship between the claimant and the defendant, or the common law of negligence due to the requirement that the claimant needs to prove both fault and causation. It was why product liability regimes were developed to address the inability of tort liability to protect consumers against dangerous products in both the US and Europe.⁸⁶ In Europe, we have the 1985 Product Liability Directive⁸⁷ which was implemented in the UK by the Consumer Protection Act 1987. In the following we focus our discussions exclusively on the Directive/CPA.

The first hurdle to bringing a product liability claim would be to define what constitutes a ‘defect’ in a ‘product’, and who is the ‘manufacturer’, in the production chain of bioprinted tissues and organs. Questions in relation to liability issues that arise here are: What are the attributable liabilities in the chain of custody of RDM bioprinting? Is a Computer-Aided Design (CAD) blueprint and computer code to be considered a ‘product’? Is an error in the digital file a product ‘defect’?

⁸⁵ See Section 3.

⁸⁶ Particularly after the Thalidomide scandal, in which the morning sickness drug of Thalidomide was found to cause damage to babies during pregnancy.

⁸⁷ European Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products OJ L 210.

4.2.1 Products and defects

Medical devices and medicinal products are both considered to be ‘products’ within the scope of the EU product liability regime. ‘Product’ defined in the CPA includes ‘a product which is comprised in other products, whether by virtue of being a component part, raw material or otherwise’.⁸⁸ Blood for transfusions was a product for the purpose of the Act. In *A and others v National Blood Authority*, it was held that the infected blood was a ‘non-standard’ product, because it contains a harmful virus.⁸⁹ The Court of Justice of the European Union (CJEU) specifically ruled in *Veedfalds v Arhus Amtskommune* that an organ for transplantation was a medicinal product.⁹⁰ The CPA only covers dangerous products and expresses that a product is defective if ‘the safety of the product is not such as persons generally are entitled to expect’.⁹¹ The ‘consumer expectation test’ refers to ‘the lack of the safety which the public at large is entitled to expect’. The ‘public at large’ is not a knowledgeable purchaser making informed decisions, but the ignorant general public.⁹² These judgments suggest that bioprinted products comprising component products will be covered by the CPA, but liability may not be expanded to include inert bioprinted implants such as nose and ear, as opposed to a functional trachea for example.

The Court can set the appropriate standard of safety in accordance with what is expected from a particular type of product. Factors for determining the standard of safety include any advertising claims, instructions or warnings that come with the product and what is reasonably expected of the product. The safety of a product is assessed by a range of considerations including instructions or warnings provided with the product (including the Patient Information

⁸⁸ Consumer Protection Act 1987, s 2(1).

⁸⁹ *A and Others v National Blood Authority and another* [2001] 3 All E.R. 289; [2001] Lloyd's Rep. Med. 187.

⁹⁰ C-203/99, [2001] EUECJ C-203/99.

⁹¹ Consumer Protection Act 1987, s 3.

⁹² Monica Navarro-Michel ‘New Health Technologies and Their Impact on EU Product Liability Regulations’, in Mark L Flear, Anne-Maree Farrell, Tamara K Hervey, and Therese Murphy (eds) *European Law and New Health Technologies* (Oxford University Press, 2013) 172-190.

Leaflet and any warning provided on packaging). Under certain circumstances, a ‘non-standard’ product might not be defective if the public accept that a proportion of such products would be flawed,⁹³ but warnings will need to be provided to inform the public of the possibility of the risk. This implies that the expectation for safety of a medicinal product is a *relative* concept.

In determining the liability of a pacemaker producer, CJEU in *Boston Scientific* held that a medical device implanted in a patient’s body must be regarded as ‘defective’, if it has the same characteristics as other devices that have been proven to have significantly higher than normal risk of failure, or in which a significant number of failures have occurred. It was possible to classify a device as defective, when it belonged to the same group or forming part of the same production series that had a defect.⁹⁴ The Court expressed that in light of the function and the particular vulnerable situation of patients, the safety requirement for those medical devices was particularly high,⁹⁵ and the notion of ‘damage caused by death or personal injuries’ under the Product Liability Directive was to be given a *broad* interpretation, in order to protect consumer health and safety.⁹⁶ This may suggest that when a defect is identified in a bioprinted product using a standard CAM process, all the bioprinted products following the same production lines (if equivalence can be established) will be susceptible to be classified as defective.

It is noteworthy that it is sufficient to establish that damage was caused by a defect in the manufacturing process; it is not required to demonstrate the specific fault within the process.⁹⁷ More recently, the Court in *Wilkes v Depuy*⁹⁸ considered whether a manufacturer is

⁹³ Richardson v LRC Products Ltd [2000] P.I.Q.R. P164.

⁹⁴ *Boston Scientific Medizintechnik GmbH v AOK Sachsen-Anhalt - Die Gesundheitskasse and Betriebskrankenkasse RWE* (Czech Republic, France, Austria, and European Commission intervening) (Joined Cases C-503/13 & C-504/13) Before the Court of Justice (Fourth Chamber) 5 March 2015 3 C.M.L.R. 6, paras 40-42.

⁹⁵ paras 37-39.

⁹⁶ paras 45-47.

⁹⁷ Carroll v Fearon [1999] E.C.C 73.

⁹⁸ *Wilkes v Depuy International Ltd* [2016] EWHC 3096 (QB); [2018]Q.B. 627.

liable for an alleged defect of an early fracture in an artificial hip made of metal components. An objective approach was set out to assessing the relevant level of safety reflecting what ‘persons generally were entitled to expect’. It stressed that the determination of a defect should be an open-textured judgment where all the relevant circumstances involved were to be considered. The Court rejected the distinction of ‘standard’ or ‘non-standard’ products and considered the relevant circumstances should include: the product’s risk-benefit balance, avoidability of the defect, whether the products was within the producer’s specification and complied with mandatory standards or regulations, warnings and instructions for use (IFU), and the involvement of a professional healthcare intermediary.⁹⁹

A range of defects in 3D bioprinted products that can give rise to liability claims include: defective anatomical scans, defective original digital design, defective digital file, defective 3D bioprinter, defective bioprinting material, human error in implementing the digital design, and human error in using (and possibly adapting) the bioprinting and materials.¹⁰⁰ Considering the health institution exemption in the MDR and the hospital exemption in the ATMPs Regulation,¹⁰¹ the threshold for a product defect may be higher for a product manufactured, modified, or used at a health institution on a non-industrial scale. It is less clear as to whether data in the 3D software scan files can count as a ‘product’, and whether errors in the CAD design file could be deemed as ‘defects’ of a product.¹⁰²

⁹⁹ paras 81-105.

¹⁰⁰ Human errors could be due to temperature control enclosure, print head nozzle obstruction, and location. It is noteworthy that in the US legal system, a surgeon is held to have the duty of inspecting the organ they are to implant, and the duty to warn their patients of the danger of the medical device, based on the ‘learned intermediary’ doctrine. The duty to examine the product is apparent particularly when serious risks are involved. The duty of inspection depends on a surgeon’s skills and experience. The scope of inspection includes: verification of product integrity – in packaging, barcode; Single European Code for tissues and cells. See European Commission, Single European Code (SEC) for Tissues and Cells [2016b] <http://ec.europa.eu/health/blood_tissues_organisms/tissues/single_european_code/index_en.htm> accessed 23 January 2019. See: MH Park, ‘For a New Heart, Just Click Print: the Effect on Medical and Products Liability from 3D Printed Organs’ (2015) *Journal of Law, Technology & Policy* 187, 207.

¹⁰¹ See Section 3.2.2.

¹⁰² European Commission, ‘Guidelines on the Qualification and Classification of Stand Alone Software used in Healthcare within the Regulatory Framework of Medical Devices’ [2016a], MEDDEV 2.1/6.

4.2.2 Who is the producer?

As discussed above, RDM in bioprinting facilitates diffusion and accessibility, yet risks as well as benefits would be re-located from central sites to local clinics and bio-manufacturing hubs. When the RDM model widens the footprint of bioprinting, it also diffuses the liabilities and risks onto a wider range of new stakeholders in the chain of custody that is required for ensuring safety and quality of both process and product. These include: CAD software engineer, clinician, surgeon, ‘qualified person’ (QP) responsible for product release for use, medical device company (in an out-sourced organisational model), and hospital. In the context of product liability, we need to ask: how to demarcate and trace the duty and risks of individual agents in the chain of custody? Who is involved in the product cycle? Is everyone involved in the product cycle potentially liable for product defects? Who is responsible for the final product? And what is the boundary between medical ‘service’ and ‘product’ in transplantation of bioprinting? Are health clinicians potentially liable for implanting a bioprinted product?

The scope of ‘producer’ is interpreted broadly which includes the manufacturer of a product and the person who wins or abstracts it.¹⁰³ Liability may also be found in anyone who is involved in the manufacturing process that adds ‘essential characteristics’ to the product. Producers of bioprinting products will be those involved in the manufacturing process that include a chain of professional healthcare clinicians working with software engineers and CAD file designers. As we mentioned earlier, it is still unclear whether errors in software code or design files would amount to a ‘defect’ in a ‘product’, and whether a software engineer or a CAD file designer should bear product liability. Are these people involved in the production chain to be deemed as ‘producer’ with equal or varying weight?

¹⁰³ CPA, s 1(2) (b). The MDR defines a ‘manufacturer’ as ‘a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and market that device under its name or trademark’. MDR, art 2(30).

The new MDR explicitly specifies that software is an ‘active device’, but it still needs further clarification as to whether software errors would constitute *product* defects and whether CAD designers can be deemed ‘manufacturer’ in RDM bioprinting. Liability is likely to arise from human errors in tinkering the CAD/CAM system and the materials to personalise 3D bioprinting implantations. There may be involved multiple digital file conversions that may result in errors. We believe that further research needs to be done to clarify, in particular, the liability of CAD file engineers in the CAM process at a health institution.

A product may be comprised of several components, in this case only the producer of the final finished product is liable. We anticipate that the safety requirements for bioprinted products are high, and the notion of ‘damage caused by death or personal injuries’ is to be given a broad interpretation. Though health clinicians and CAD software engineers may be held vicariously liable for product liability in torts, it may be sensible to suggest that only the producer of the final finished bioprinted product is liable under CPA, if it is comprised of several components. While it is difficult not to envisage transplantation to human body as a ‘service’, it is still unclear what is to be considered the ‘final’ bioprinted product, prior to transplantation to human body.

It is also noteworthy that the CPA provides legitimacy defences for producers. Producers can be cleared of liability if they can prove that they did not place the product ‘on the market’,¹⁰⁴ or ‘put into service’.¹⁰⁵ Notably, the CPA embeds a ‘development risks defence’, which allows a defence where the risks of a product could not be identified with the state of scientific and technical knowledge at the time. The ECJ concluded in *European Commission v United Kingdom* (1997) that:

¹⁰⁴ ‘Placing on the market’ means ‘the first making available of a device, other than an investigational device, on the Union market’. MDR, art 2(28).

¹⁰⁵ ‘Putting into service’ means ‘the stage at which a device, other than an investigational device, has been made available to the final user as being ready for use on the Union market for the first time for its intended purpose’. MDR, art 2(29).

‘The state of knowledge must be construed so as to include all data in the information circuit of the scientific community as a whole, bearing in mind, however, on the basis of a reasonableness test, the actual opportunities for the information to circulate’.¹⁰⁶

‘The state of scientific and technical knowledge’ is a fluid concept, but the ECJ said the standard was that of the most advanced research, and once an isolated opinion suggests there might be a risk, the risk cannot be said to be unforeseeable. The ‘development risks defence’ may thus be a possible defence for 3D bioprinting product providers given the evolving state of the art.

Another question in the 2D regulatory landscape is the role of standard/regulation compliance in product liability claims. Suppose that the manufacture and use of a 3D bioprinting product is fully compliant with the *ex ante* regulatory regime, then is *ex ante* regulatory compliance a complete defence to any *ex post* product liability claim? It was held in *Wilkes v Depuy* that regulatory compliance is not an automatic defence in the CPA, nor even a *prima facie* defence as in the US, yet such circumstance may provide strong evidence on the appropriate level of safety of the product.¹⁰⁷ Particularly, the Court expressed that:

‘[n]on-compliance with any appropriate mandatory standards will provide evidence of defect; and that compliance with such standards, whilst not providing a complete defence, will provide evidence that, in respect of the matters to which those standards go, the level of safety required by the Act has been satisfied and the product, in those respects, is therefore not defective’.¹⁰⁸

It is also worth noting that the European Commission in 2017 launched the evaluation of the Product Liability Directive. In particular, it attempts to examine the current product liability

¹⁰⁶ *European Commission v United Kingdom*, C-300/95 [1997] ECR I-2649.

¹⁰⁷ *Wilkes v Depuy*, para 101.

¹⁰⁸ para 97. For more discussions, see: Richard Goldberg, *Medical Product Liability and Regulation* (Hart, 2013) 161-165.

regime in relation to recent digital development. Questions are tackled such as whether apps and non-embedded software are ‘products’ as defined in the Directive; whether an unintended, autonomous behavior of a robot could be a ‘defect’; and how the strict liability for damage is allocated when there are multiple participants in the production chain. It also sets out to clarify liability at each level of automation,¹⁰⁹ so this evaluation may well impinge on the digital features of the bioprinting case.

We can see that, again, the deficiencies in the *ex post* liability and compensation regime are not so much a gap as a series of interpretative uncertainties. It appears that the law has struggled to meet the changing faces of biotechnology by constantly stretching and reconfiguring the legal context. With the provisional ‘process-based’ regime and the review mechanisms in place, at this stage bioprinting may not necessitate a bespoke piece of regulation. Regarding the legal uncertainties, at the *ex post* phase we believe that the ‘co-regulation’ approach would best serve to clarify the ambiguities with a view to striking a healthy balance between safety and innovation.

4.3 The key insights for the biofabrication field

In summary, some key insights could be passed on to other areas of biofabrication from our investigations on both the *ex ante* and *ex post* dimensions of the bioprinting regulatory landscape. Before the full maturity of product development and business models, the first step would need to ascertain whether a novel process has introduced novel products which require a period of ‘wait-and-see’. If the novel manufacturing process has significantly changed the safety profile of a product, we suggest that a provisional process/product approach to regulation in the initial phase would be fit for purpose. However, a provisional process/product approach

¹⁰⁹ European Commission, Evaluation and Fitness Check (FC) Roadmap, Evaluation of the Directive 85/374/EEC concerning liability for defective products [2016-17]. <http://ec.europa.eu/growth/content/public-consultation-rules-liability-producer-damage-caused-defective-product-0_en> accessed on 7 January 2019.

would require ongoing reviews and monitoring of new scientific data and diverse stakeholder involvement with a view to reconfiguring the respective roles of government, intermediaries, and the industry, for an optimal governance model. It remains to be seen if the current ‘Hospital Exemption’ or the ‘Specials’ routes will continue to sit well with other different types of biofabrication.

We expect a responsive co-regulation approach would be key to both the *ex ante* and *ex post* dimensions of regulation, as it is well-placed for interpreting legal uncertainties arising from the complex of processes and products, classifications, market approval pathway, ongoing monitoring and review, and liability and compensation regimes (See Table 4.3). This table summarises the process/product, existing regulation, and co-regulation approaches that we have considered.

Biofabrication regulation	Ex ante (before authorisation)	Ex post (after authorisation)
Focus	Safety	Liability and compensation
Process/product regulation	<ul style="list-style-type: none"> • Classification • Whether to adopt a provisional process approach to regulation? 	Whether, when, and how to adapt to a product-based approach?
Existing regimes and key issues	Tissues and Cells; Medical Devices; Pharmaceuticals; and ATMPs <ul style="list-style-type: none"> • Market approval pathway • Hospital exemptions; Specials 	Product Liability Directive; Contract, Tort liability, and the Consumer Protection Act <ul style="list-style-type: none"> • The definition of product and defect in anatomical scans and design files • The definition and liability of producer
Co-regulation model	<ul style="list-style-type: none"> • Big Data/Big Government; Intermediaries’ oversight; Self-regulation • RRI • NEST-ethics 	
	Multi-stakeholder involvement	<ul style="list-style-type: none"> • Multi-stakeholder involvement • A duty to ongoing review • Post-market surveillance
A new bespoke regime?	To be decided after sufficient data are gathered and assessed for a complete risk profile	

Table 4.3. Biofabrication regulatory scenarios

5. Conclusion

Due to the novelty, complexity and technical specificity of 3D bioprinting, it presents a range of unprecedented quality and safety challenges from a manufacturing ‘*process*’ perspective, as

well as challenging existing product regulation regimes. We have examined the extent to which RDM in 3D bioprinting disrupts existing laws and regulations in both *ex ante* and *ex post* dimensions. It appears that the deficiency here is not so much as a gap as a series of interpretative uncertainties.

In order to map the gaps and uncertainties of redistributed 3D bioprinting in the regulatory sphere, relevant EU/UK legal instruments have been analysed. It is unclear whether bioprinted products, repeated using the same manufacturing equipment or process but customised for individual patients, will be regarded as operating in an industrial or craft-like manner, and to what extent the existing ‘Hospital Exemption’ and ‘Specials’ regulatory product routes might accommodate redistributed 3D bioprinting.

The introduction of CAM greatly facilitates redistributed bioprinting, but corresponding challenges relating to the duties and liability of CAD file designers, data control, data management, data protection, and privacy issues, remain to be addressed. A RDM model in bioprinting appears to favour a third-party bioprinting unit on site. At the time being it seems unlikely that hospitals and health institutions will stretch its nature as a manufacturer once incorporating bioprinting in situ.

At present, we do not see an urgent need to develop a bespoke regulatory regime for biofabrication. We review the past trajectories of GMOs and nanotechnology, and suggest a processual ‘process-based’ approach to bioprinting, facilitated by the co-regulation model, is best fit for purpose during the early development phase of bioprinting. The provisional ‘process-based’ approach will serve as a safety valve to temper the tension between innovation and safety. After the risk profile of the technologies is complete, and standardisation of the industry is well developed, regulators, intermediaries, industries and participating stakeholders could make an informed decision as to whether, when and how to transit to a ‘product-based’ regime.

Overall, the regulatory landscape for bioprinting as well as the technology *per se* are still restructuring and reconfiguring their positions through redefinition of extant concepts and exemptions. There remain significant legal and regulatory uncertainties in a number of applicable and inter-related issues: process and product liability; the definition of the manufacturer; the respective roles of surgeons, software designers, manufacturers and others; the status of software and bioprinting equipment; the complexity of product regulation and the important relevance of exemptions in current regimes; how bioprinting as ‘medical innovation’ might redefine the traditional craft status of ‘practice of medicine’; and how different software management strategies will impact on the field. The effects of Brexit remain to be seen in relation to how the UK regulations would diverge from or mimic the current EU regime. Here we envisage that a co-regulation approach would serve to clarify these gaps, uncertainties and problems by ongoing review, data gathering, and multi-stakeholder involvement. This involves real-time communications amongst regulators, producers, users, intermediaries, and the general public to invigorate the extant legal regime ready for the challenges confronted by new technologies.

Acknowledgements

The authors would like to thank Professor Roger Brownsword, Dr James Griffin, and Pheh Hoon Lim, for their comments on an earlier draft of the paper, and Katy Joyce for her research assistance. All errors remain the authors’. This work is supported by the UK Engineering and Physical Sciences Research Council project ‘3DP-RDM: Defining the Research Agenda for 3D printing-Enabled Re-distributed Manufacturing’ [EP/M017656/1] and the UK Economic and Social Research Council project ‘Biomodifying technologies and experimental space: organisational and regulatory implications for the translation and valuation of health research’ [ES/P002943/1]. This article is based on the report ‘A feasibility study of mass customisation

governance: regulation, liability, and intellectual property of re-distributed manufacturing in 3D bioprinting'. All data created during this research are openly available from the University of Cambridge data archive at: <https://capturingthevalue.wordpress.com/3dp-rdm-reports/>.

End of text