

3D Bioprinting Regulations: a UK/EU Perspective

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Abstract

This report introduces the challenges 3D bioprinting poses to the existing legal regime across bioethics, safety, regenerative medicine, and tissue engineering. We briefly review the 3D bioprinting technology and look into the relevant regulatory instruments for the pre-printing, printing, and post-printing stages. Special attention is paid to the applications of the EU Advanced Therapy Medicinal Products Regulation and the new Medical Device Regulation.

I. INTRODUCTION

With the technological breakthrough in additive manufacturing (AM, aka, three-dimensional printing, 3D printing), 3D bioprinting technologies have emerged as an efficient tool for tissue engineering and regenerative medicine by adopting computer-aided manufacturing (CAM) into healthcare delivery. The disruptive nature of the 3D bioprinting technologies not only weaves a dream of “printed-organ-on-demand”, but also challenges the traditional regulatory framework.

There is not currently a sui generis regulatory regime governing the whole bioprinting process, but piecemeal legislation is relevant in relation to tissue engineering and regenerative medicine. Regenerative medicine using cell or tissue engineering is considered advanced therapy in the European Commission (EC) Regulation on Advanced Therapy Medicinal Products (ATMP).¹ The principles developed in the ATMP Regulation are applicable to 3D bioprinting. Relevant legal instruments include the ATMP Regulation, the EC Tissues and Cells Directive,² pharmaceutical

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¹ Council Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products, amending Council Directive (EC) 2001/83/EC (ATMP Regulation).

² 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 (EUTCD, or the Parent Directive).

regulations,³ and the new Medical Device Regulation,⁴ all being applicable at different stages of production.

The product development of 3D bioprinting technologies involves “Re-distributed Manufacturing” (RDM), which means that the manufacturing process is taking place at several technical stages at multiple sites rather than at a single central manufacturing plant.⁵ Various factors will affect the quality of materials and products. Quality assurance and testing is required at every stage of manufacturing before moving onto the next site for further processing. Hence, this section will analyse associated issues arising from each step in the manufacturing process: pre-printing, printing, post-processing, and testing and characterisation.

II. BIOPRINTING TECHNOLOGY

3D bioprinting technology is primarily driven by three factors: the quality of bioprinters and source materials, computer-aided design (CAD) software, and advances in the science and application of regenerative medicine. Regenerative medicine means using the self-healing processes of the human body by therapeutic products of tissue and cell engineering, which is the process of generating repair tissues and organs (bioartificial tissues) using cells from an individual patient (to create tissues outside the body and then implant them). The advantage of using a patient’s autologous cells rather than donor biomaterial is that it reduces the risk of tissue rejection.

The following are the steps involved in using a bioprinter with autologous cells: collect and grow stem cells or mesenchymal (multipotent) cells from patient biopsies; make “bio-ink” from enough cells and load into the cartridge; use the bio-ink and a hydrogel-carrying medium to print tissues guided by software and a bioprinter; the printed tissues are left to mature for several weeks.⁶ After maturation, the printed tissues can be used in medical research, new drug testing, or as a transplant material. 3D bioprinted organs are anticipated to relieve the shortage of transplantable organs, thus preventing the complications of sources and commercialisation of human organs. Meanwhile less complex clinical applications such as bioactive nasal prostheses are being developed. It is expected that in the near future such a bioprinter could be an essential tool for in-vivo printing in the hospital operating theatre.

III. BIOPRINTING REGULATIONS

Bioprinting is a subcategory of 3D printing though the same regulation rationale cannot be applied due to the inherently different policy considerations for protecting human

³ Council Directive (EC) 2009/120 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use as regards advanced therapy medicinal products [2009] OJ L 242/3.

⁴ Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, Brussels, 15, June 2016, 9364/3/16 REV 3; Revisions of Medical Devices, available at <https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision_en> (accessed 31 March 2017).

⁵ P Hourd, et al., “A 3D-bioprinting Exemplar of the Consequences of the Regulatory Requirement on Customized Process” (2015) 10(7) *Regenerative Medicine* 863–883.

⁶ “Printing a Bit of Me”, *The Economist*, 8 March 2014, available at <<http://www.economist.com/news/technology-quarterly/21598322-bioprinting-building-living-tissue-3d-printer-becoming-new-business>> (accessed 31 March 2017).

health and safety. These range from the fundamental philosophical and bioethical issues to practical risk, biosafety and security concerns. 3D bioprinting presents the recurrent risks and challenges arising from implantable medical devices, cell therapy, stem cell therapy, and organ transplantation. Safety issues include sources of biomaterials, unhealthy donors, implant efficacy, and post-transplant infections.

Current regulatory regimes on cell therapy and stem cell research lack clarity when considering their application to bioprinting regulation. The legal uncertainties of bioprinting are further compounded by the multiple actors involved in the supply and production chain. Specifically, the adoption of CAM in bioprinting (through which CAD software is used to customise the product to an individual patient and to trigger the bioprinting process) further complicates the legal landscape.

1. Source of materials

Researchers have long been culturing and reproducing cells in laboratories, including skin tissues, blood vessels, and other cells from various organs. There is a wide range of materials that could be used in bioprinting. In addition to cells and collagen, autologous stem cells are an attractive option for use as bio-ink for printing different organs and tissues, as they may adapt easily to host tissues.

The 3D bioprinted product using bio-ink developed from autologous cells would reduce the patient's rejection rate, though in certain circumstances it is also possible to use allogeneic cells for fabrication. Cells and tissues are first acquired from a patient or a donor before the initial processing of cell releasing from tissue matrix, cell isolation/enrichment, cell culture, harvest, and encapsulation of cells in hydrogel.⁷ In order to ensure the quality and safety of cell and tissue material, the early stage of donation, procurement, and testing of tissue and cells is governed in the UK by the Human Tissue Act 2004 (following the EU Tissues and Cells Directive (EUTCD) 2004/23).⁸ This Directive is applied through two separate implementing Directives: the First Technical Directive covering the actions just listed⁹ and the Second Technical Directive covering storage and distribution of tissues and cells.¹⁰ In fact, a third Directive was introduced later, in 2012, making amendments in particular with respect to testing regimes.¹¹

Establishments carrying out the above activities are required to meet the standards that are detailed in the Guide to Quality and Safety Assurance of Human Tissues and Cells for Patient Treatments, as implemented by HTA Directions 003/2010. "HTA Directions 003/2010" consolidate and clarify the standards required under the Human Tissue (Quality and Safety of Tissues and Cells for Human Application) Regulations 2007.¹² These directions concern especially the requirement for clean processing environments, quality control processes for source materials and their storage, responsibilities of

⁷ Hourd, et al, *supra* note 5.

⁸ European Directive 2004/23/EC (Parent Directive).

⁹ The First Technical Directive (European Directive 2006/17/EC).

¹⁰ The Second Technical Directive (European Directive 2006/86/EC).

¹¹ The Third Technical Directive (European Directive 2012/39/EU).

¹² HTA website, <<https://www.hta.gov.uk/>> (accessed 31 March 2017).

production managers, traceability, and protocols for record-keeping and inspection by regulators.

Regulation of biotechnology is based upon principles of bioethics such as “do no harm”, confidentiality, informed consent, and benefit sharing. According to the Human Tissue Act 2004, only a licensed person is allowed to remove a living person’s transplantable material. Such removal would need to be non-commercial. A full informed consent process should minimise the risk of harm and possible violation of ethical considerations. Express consent from the donor is required to remove, store, and use his or her tissues. Consent could be given by the donor (in his/her lifetime or after death if such consent is expressed by will), a nominated person, or the next of kin. A child is to give consent him/herself but, in situations where a child is incapable of giving consent or where it involves the mentally incapacitated, a parent or guardian is to give express consent. Consent will not be required if the donor or the next of kin could not be traced. The ethics committee may approve the research without consent. Donors should be informed of the current and future use of his or her cells and tissues. It is suggested that complete details about the composition of the bioprinted product, the implantation process, all conflicts of interest, and all potential outcomes and adverse effects are noted in the consent form.¹³ It is noteworthy that a “presumed consent” (opt-out) model of the deceased is applied in Wales.¹⁴

In preparation of the materials for fabrication, the use of Human Embryonic Stem Cells (HESCs) as bio-ink once again touches on the social and religious taboos of cloning, and the interpretation of humanity and human dignity. The ATMP Regulation states that the regulation of ATMP at EU level should not interfere with decisions made by individual member states on whether or not to allow the use of any specific types of human cells, such as embryonic stem cells or animal cells (i.e the principle of subsidiarity). In view of potential objections, researchers may now pursue the more recently developed “Induced Pluripotent Stem Cells” (iPSC) technologies, or collect multipotent stem cells (adult/somatic stem cells) for producing pluripotent stem cells for 3D tissue engineering in order to bypass the destruction of human embryos.

The ATMP Regulation also acknowledges the respect of fundamental rights by making reference to the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicines: Convention on Human Rights and Biomedicine. It is recognised that the same regulatory principles for other types of pharmaceutical medicinal products should be applicable to ATMP where they are comparable, and that specific technical requirements with regard to quality and clinical data to ensure quality, safety and efficacy, may also be required. The central Committee for Advanced Therapies (CAT), which implements the ATMP Regulation by assessing newly-notified products, acts as an advisory body to the over-arching European Medicines Agency. The ATMP Regulation stresses that the procurement of human cells or tissues used in ATMP should

¹³ M Varkey and A Atala, “Organ Bioprinting: a Closer Look at Ethics and Policies” (2015) *Wake Forest Journal of Law and Policy* 275, 288.

¹⁴ JF Douglas and AJ Cronin, “The Human Transplantation (Wales) Act 2013: an Act of Encouragement, Not Enforcement” (2015) 78(2) *Modern Law Review* 324.

be derived from voluntary and unpaid donation, and that the anonymity of, and solidarity between, donor and recipient should be respected.

2. Bioprinting triggered by computer-aided manufacturing

The printing process is triggered by the instructions generated by CAD or CAM systems. The customised CAD file is generated by 3D scanning and image segmentation. The medical use of 3D printers involves a digital file generated from 3D scanning of a human body part, and reprinting at the wound site for repair. In medical use, researchers could use the digital data acquired from Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) scans to make a 3D design model of an organ or other tissue. It is then used in the software designing process in order to modify the design for customisation. The next step is to convert the design or data into an STL file. The STL file is then imported into the printer software package to set up the machine for printing. It is then to be reviewed and verified by a surgeon to make possible patient-specific tailoring decisions, before triggering the CAM process.

Mass digitisation and dissemination of STL files poses risks to the regulatory framework of consumer safety, product liability (quality control), and data protection, confidentiality, and safety. A major issue is that the design involves multiple translation and compilation steps between different software applications, each having different error sensitivities, hence errors in customisation settings are likely to occur. The current computer-aided process planning still relies on human expertise and manual interaction so that the manufacturer will need to verify and account for the accuracy of the image.¹⁵ These errors would consequently have direct impact on the mechanical strength of the finished 3D bioprinted product. A key question, then, is how could the translation and compilation steps better ensure reproducibility and comparability of printed products?

It is also noteworthy that if the software and hardware set-ups for bioprinting are regarded as “medical devices” that fall within the auspices of new EU Medical Device Regulations (MDR),¹⁶ then they will need certification before being released on the market. Once a software is qualified as a medical device (as it should be if it affects medical decision-making) it will fall subject to safety and performance requirements when used for diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or disability, and the “investigation, replacement or modification of the anatomy or of a physiological or pathological process or state”.¹⁷ With regard to the classification of the software as a medical device, the new MDR further explains that standalone software that drives a device will fall into the same class as the device. But if standalone software is independent of any other device, it is classified in its own right.¹⁸ The use of software in the process raises data protection issues. Extra caution needs to be paid to the protection of personal data. Information for documentation should include: manufacturing parameters; risks identified for each step of the manufacturing process;

¹⁵ Hourd et al., *supra* note 5.

¹⁶ Art. 18a, Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, 9364/3/16 REV 3, Brussels, 15 June 2016 (MDR).

¹⁷ *ibid* Art. 2(1)(1) MDR.

¹⁸ MDR, Annex VII Section II.3.

mitigations of these risks; software steps; validation and testing steps, and acceptance activities.¹⁹

3. Bioprinted medical products

The key issue in post-printing is the classification of a bioprinted product: since organs and tissues are not “original” body parts are they to be regulated as “products”, medical devices, drugs, ATMP, or a new category? Further, when the printing process takes place at clinics or hospitals are they put “on the market” or “put into service”? The European Medicines Agency (EMA) is responsible for the regulatory framework, while the CAT acts as the scientific Committee dealing with individual submission of new proposed products. The CAT will decide the classification and evaluate the quality, safety and efficacy of an ATMP product in accordance with the scientific information submitted to the Committee.

The ATMP Regulation classifies tissue-based or cell-based products as medicinal products including gene therapies, cell therapies, and tissue engineering,²⁰ which may or may not be regarded as regenerative medicines, a non-legal category. Many bioprinted implants will be classified as tissue-engineered products (TEPs) under the ATMP Regulation (which provides Europe’s first legal definition of TEPs), which will typically combine a cellular component with a supporting matrix of hydrogel. Cells or tissues that are subject to “substantial manipulation” are considered “engineered” and thus fall within the ATMP classification.²¹ The ATMP regulation involves one centralised marketing authorisation pathway, or an alternative “hospital exemption” route of individual therapies under a medical practitioner’s prescription not produced “routinely” or by an “industrial method”, the aim being to separate one-off treatments to address unmet individual needs from products that could be commercialised and placed on the open market.²² The ATMP regulation waives the requirement of pre-market approval under the “hospital exemption” where the ATMPs are prepared on a non-routine basis according to specific quality standards. Due to the experimental nature of this, so far the bioprinted products are used via this “hospital exemption” (a similar though not identical scheme is called “Specials” in the UK²³). However, some aspects of its application remain unclear, especially the question of whether bioprinted products, which combine some standardised processes (e.g. in the software and machinery) with unique individual cells, will be deemed to be “routine” or “non-routine” manufacturing – an important factor for determining the regulatory measures and data requirements.

The production of ATMPs should follow the principles of good manufacturing practice, and good clinical practice when conducting clinical trials. If producers seek to market a product, clinical trials on ATMPs are required for central EMA market authorisation. It is also noteworthy that a “combined” ATMP, comprised of both medical device and viable cells or tissues, will require pre-market approval from the EMA, which

¹⁹ MDR, Annex II Technical documentation.

²⁰ Art. 2(1)(a) ATMP.

²¹ Art. 2(1)(c) ATMP.

²² Recital (6) ATMP.

²³ “Supply unlicensed medicinal products in the UK (Specials)”, available at <<https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials>> (accessed 31 March 2017).

involves assessment for both the medical device part and the medicinal product part. After the bioprinting process, traceability of the patient and the ATMP is required to monitor the safety of ATMP. It is required that the holder of marketing authorisation keeps the relevant data for a minimum of 30 years after the expiry date of the product for follow-up of efficacy and risk management post-authorisation.²⁴ This places a significant onus on producers, hospitals and even physicians in data collection and storage, depending on where the liability is determined to lie.

IV. FUTURE TRENDS

The emergence of 3D bioprinting presents a potentially useful tool for tissue engineering and regenerative medicine that is attracting a great deal of development effort, yet the novel production methods and the products themselves challenge the existing boundaries in the healthcare regulatory sphere. It remains to be seen whether the “mass customisation” that bioprinting allows will find the EU ATMP Regulation and the new Medical Device Regulation sufficient for bioprinting regulation, or how the existing laws might require adaptation to meet the challenges of bioprinting. It is expected that public debates will need to take place in the near future on the development pathway of the technology, and the regulatory status of its processes and products. Policymakers will also need to make an informed decision on whether to have bioprinting products and services covered by national or private health insurance.

²⁴ Art. 15(4) ATMP.