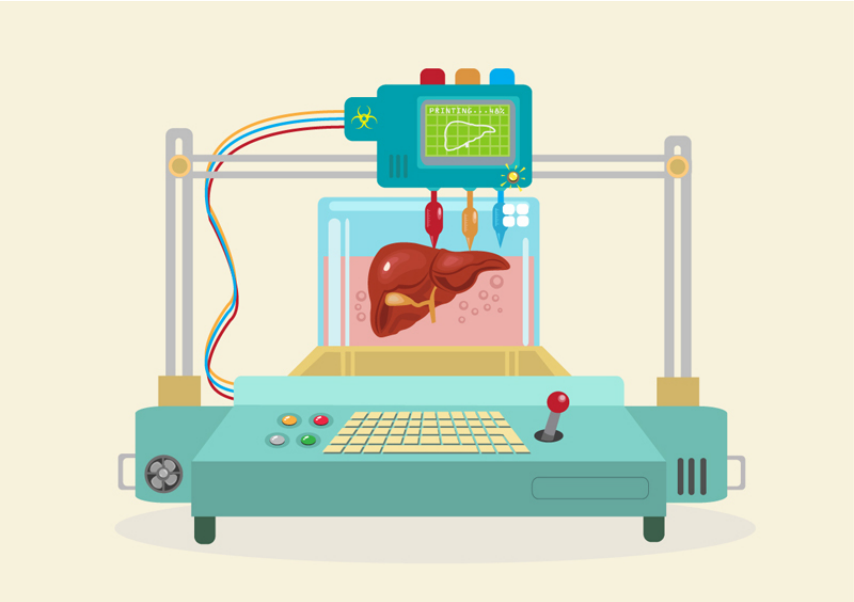
European Parliament

3D bio-printing for medical and enhancement purposes: Legal and ethical aspects



IN-DEPTH ANALYSIS

Science and Technology Options Assessment

EPRS | European Parliamentary Research Service
Author: Mihalis Kritikos
Scientific Foresight Unit (STOA)
PE 614.571

3D bioprinting for medical and enhancement purposes: Legal and ethical aspects

July 2018

Abstract

The aim of this In-depth Analysis is to illustrate the different ways in which the current EU legislative framework may be affected by the emergence of 3D printing for medical and enhancement purposes and the respective technological trends. Building upon the STOA study 'Additive bio-manufacturing: 3D printing for medical and human enhancement', it analyses the issues that might have to be dealt with, identifying the European Parliament committees concerned and the legislative acts that might need to be revisited, especially in view of the recently adopted report and resolution on Three-dimensional printing, a challenge in the fields of intellectual property rights and civil liability (2017/2007(INI)).

This analysis also provides a series of overarching recommendations that EU actors may wish to take into account when dealing with 3D bio-printing, resulting from an examination of the multiple ethical and legal challenges associated with this emerging technology has been performed, along with a scan of current legislation in a wide

PE 614.571

This document is based on and draws upon the STOA project 'Additive bio-manufacturing: 3D printing for medical recovery and human enhancement'. The project was requested by the European Parliament's Science and Technology Options Assessment (STOA) Panel. It was carried out by the European Technology Assessment Group (ETAG), led by the Institute for Technology Assessment and Systems Analysis at Karlsruhe Institute of Technology (KIT/ITAS) and including the Institute of Technology Assessment of the Austrian Academy of Sciences (ITA/OEAW), the Rathenau Institute, the Danish Board of Technology (DBT) Foundation and France-based Responsible Technology (RT). It was managed by the Scientific Foresight Unit (STOA) within the Directorate-General for Parliamentary Research Services (DG EPRS) of the European Parliament.

AUTHOR

Mihalis Kritikos
Scientific Foresight Unit (STOA)
Directorate for Impact Assessment and European Added Value
Directorate-General for Parliamentary Research Services
European Parliament, Rue Wiertz 60, B-1047 Brussels

LINGUISTIC VERSION

Original: EN

ABOUT THE PUBLISHER

To contact STOA or to subscribe to its newsletter please write to: STOA@ep.europa.eu
This document is available on the internet at: http://www.ep.europa.eu/stoa/

Manuscript completed in July 2018

DISCLAIMER

PE 614.571
ISBN 978-92-846-3148-3
doi 10.2861/923327
QA-01-18-636-EN-N

Table of contents

1. Introduction

Three-dimensional printing in its biomedical form faces significant regulatory and socio-ethical challenges. The complexity and customisation of additive bio-manufacturing (bio-AM) artefacts trigger the need for an assessment of the appropriateness of EU rules in the domain of pharmaceuticals, medical devices, advanced therapies, tissues and cells, organs, blood, food and chemicals. Given the decentralised character of the 3D bio-printing process and the potential rise of consumer-producer ('prosumer') additive (home) bio-manufacturing, the main regulatory challenge is in defining and categorising the processes and products associated with 3D bio-printing. Moreover, developments in bio-AM, including data sharing, DIY practices and customised risk-related products, may eventually bring current medical practices into the domain of the protection of intellectual property rights (IPR) and data ownership under pressure.

The issue of ownership is closely linked to patients' data and materials, and covers questions of personal ownership of identity and health data (which are needed to create other devices and may therefore foster innovation), as well as the use of data to stimulate non-therapeutic applications. Three dimensional printing also raises legal challenges in relation to the protection of data, intellectual property (IP) and privacy. For example, we might consider risks associated with storing and using very personal physical or medical information. In the frame of 3D bio-printing, creating a customised medical device may mean that several different actors in a decentralised supply chain have access to very specific details and perhaps images pertaining to the patient's body, conditions and preferences. Illegal file sharing amongst some communities – with blueprints for objects unlawfully traded in the same way as MP3 or video files – might present an additional threat to IP protection.

As personal 3D printers become more powerful and common, and as independent service providers grant access to increasingly sophisticated printers and produce replacement parts and other potentially harmful products, decentralisation of manufacturing will increase and move manufacturing away from centralised control, potentially leading to more private R&D endeavours, and a re-balancing of knowledge sharing and production between public and private sectors. It is clear that this will have broader implications in many areas of currently applicable laws, such as criminal law, regulatory law and environmental and constitutional law. Safety regulations are likely to be affected, becoming increasingly irrelevant or outdated, as well as, in the context of medical-ethical rules in relation to informed consent, access to care, autonomy, quality and safety standards, protection of vulnerable groups, protection of medical data, clinical effectiveness and good care. In the bio-printing area, with its strong impact on sensitive goods and values, such as human rights, health, integrity and dignity, this is a particularly challenging development.

Many emerging applications of bio-AM are difficult to fit into current legislative pillars or categories. Moreover, one of the key challenges in regulating AM is acknowledgement of the fact that biological and non-biological materials are regulated in different ways. Additive manufacturing applications however are often considered combination products that include both biological and non-biological components. When these biological materials are human or human stem cell derived, both ethical concerns and needs for public policy scrutiny tend to increase. The introduction of 3D bio-printing is expected to affect policies on the use of substances of human origin, such as human tissues and cells, blood and organs. The combination of materials (devices) and human biological material, in combination with alternative manufacturing processes for AM, may also create inequality in access to therapies and services. Engineering of artificial organs would first and foremost alleviate the shortage of donor organs that are required. It could also put an end to illegal trade in human organs. Additionally, the technology allows the use of autologous material, i.e. material that derives from the patient, meaning the immune system would be less likely to reject an organ created from the patient's own cells.

2. Legal considerations

2.1. Legal classification of 3D printing

Three dimensional bio-printing, like every new or emerging technology raises questions about the exact legal nature and specific categorisation of bio-printed materials or 'bio-printers' as machines used for a medical purpose. The legal classification of 3D bio-printing products is crucial, however, given that different rules applying to biological and non-biological materials can lead to complications for combined products, such as a 3D-printed scaffold on which living cells are cultivated. Nevertheless, the selection of a particular legal basis, such as that provided by the Advanced Therapies Regulation, may prove to be a significant regulatory burden in terms of its market approval requirements.

At the same time, the legal classification of 3D printing is extremely difficult due to its custom-made character (as it facilitates the production of standard devices that can be adapted to the features of the patient and medical devices that are unique for one patient),[1] and the blending of biological and non-biological components in the frame of the production process. The existing legal framework, such as the In Vitro Diagnostic Device Regulation 2017/746, does not provide any particular guidance on these distinctions, as its provisions do not state clearly how substances of human origin should be judged.

Due to the combination of materials and processes used in AM, current established pillars of EU regulation (pharmaceuticals, medical devices, advanced therapies, tissues and cells, organs) may be unsuitable for bio-AM regulation in medicine and therefore require re-evaluation. For instance, it is unclear whether bio-printing applications constitute a biological product (since the interaction with the body is more 'natural' during their use) or a non-biological component, whether they are a medical device or an advanced therapy.

The final product of 3D bio-printing may defy existing definitions, as this could be a medical device or an accessory to a medical device, regulated under Directive 93/42. The product can also be an Advanced Therapy Medicinal Product (ATMP), regulated under Regulation 1394/2007, or even a medicinal product, regulated under Directive 2001/83. As for the raw material, it may be chemical substances that are regulated under Regulation 1907/2006 (REACH), or living cells and tissues regulated under Directive 2004/23. It should also be noted that special rules apply to medical devices manufactured using animal tissue (Commission Regulation 722/2012). Raw material for medical devices and medicinal products are regulated whilst harvest, storage, transport and use of biological material is regulated under EU law. In relation to the production process, a quality system is required for the manufacturing process of medical devices and medicinal products, whilst national competent authorities and notified bodies may classify design and production tools as medical devices, e.g. design software.

Any attempt to classify 3D printed products requires a separate qualification regarding the 3D printer, design software and the input material. First, the 3D printer itself is considered an advanced manufacturing technology, and as such is qualified as a production tool, rather than as a medical device falling under the scope of the EU Machinery Directive 2006/42, that sets conformity requirements guaranteeing standard levels of safety. The regulatory status of software depends on its intended purpose, as well as on whether the software is placed on the market or put into use for the end-user. Design software cannot be classified as a medical device if it does not have a specific medical purpose and is not placed on the market. With regard to the input material, the intended purpose of the material determines its qualification. If the intended purpose of the input material is to manufacture a medical device, then the input material itself may also be considered a medical device and will require

[1] The result of production is a truly unique device made by an expert (dental technician, orthopaedic shoemaker, etc.) that is made only once for the specific patient indicated in the prescription.

CE marking. This was the case, for example, in the medical gasses market where generic (industrial) gasses (i.e. oxygen) are considered either medicinal products or commodity gasses, depending solely on the intended use.

The classification of 3D bio-printing mainly depends on whether 3D printed medical devices are mass-produced or custom-made in terms of being produced on an individual/small scale, as well as on whether the products fall under the definition of in-house manufacture when they are printed by the actual user, such as a hospital. In current practice, customisable and unique 3D printed medical devices are regarded as custom-made devices under the Medical Devices Directive and enjoy a low regulatory burden as not subject to ex-ante oversight controls, normal quality system requirements or conformity assessment requirements. Due to their customised character (produced in accordance with a specific prescription for a specific individual), there is no requirement for CE marking or conformity assessment.

Such medical devices are subject to the – rather light – Annex VIII statement requirements, with the only safeguards being manufacturer diligence, prescription by a qualified person, and ex-post controls exercised by competent authorities. According to Article 11, para. 6 in the case of custom-made devices, the manufacturer shall follow the procedure referred to in Annex VIII and draw up the statement set out in that annex before placing each device on the market. In other words, custom-made devices, being mostly one-off devices, are exempted from conformity assessment and subsequent CE marking and are only subject to ex-post controls by the competent authorities.

At the same time, it should be noted that with the rapid advent of 3D printing, it has become possible to produce highly individually customised devices in a way that can potentially be standardised or scaled without limitation. In that regard, 3D printing is similar to 'normal' production techniques. Given the scalability of 3D printing to controlled standardised production processes, the question is whether the repeatability and standardisation of 3D printing of devices triggers the needs to view 3D printing of medical devices as 'normal' production of devices with a high degree of customisation in the production process, rather than custom-made devices. The Medical Devices Directive makes a special reference to the need for all devices that are mass-produced by means of industrial manufacturing processes not to be considered as custom-made devices.

The recently adopted Medical Devices Regulation (MDR) 2017/745 does not specifically regulate 3D printed medical devices, nor the 3D printing manufacturing process. Under the Regulation, custom-made devices will retain a lower regulatory burden although requirements for manufacturers (Article 10) are applicable to all manufacturers, including those manufacturing custom-made devices. At the same time, the new Regulation retains the same requirements and definitions of custom-based devices. A custom-made MD is defined as a device that: (i) is prescribed by a qualified healthcare professional – whose written prescription should include specific design characteristics of the MD; and (ii) is intended to be used by only one patient to meet their proper medical needs (Article 2 of the Regulation). The manufacture of 3D printed MD (i) according to the anatomical characteristics of a patient, (ii) in order to meet their individual needs, would likely to be qualified as a 'custom-made' device. Such status benefits from a legal framework whose placement on the market is less constrained than that related to the general regulation of MD.

Indeed, manufacturers of custom-made devices shall only be bound by an obligation of conformity assessment procedures upon which the device shall be compliant with safety and performance requirements (Articles 10, 20 and 21 of the Regulation). These medical devices are therefore not required to affix CE marking: a significant and constraining procedure demonstrating the safety and the performance of the device for the patient. The Regulation states that without prejudice to national provisions regarding professional qualifications, manufacturers of custom-made devices may demonstrate the requisite expertise referred to in the first subparagraph through at least two years of professional experience within a relevant manufacturing field. Additionally, manufacturers of Class III custom-made implantable devices shall be subject to the conformity assessment as specified in Chapter I of Annex IX.

Based on the above, a series of questions arise: can a 3D printer be considered as a means to enable large-scale production and replacement of an industrial process? Can a hospital which manufactures many of those devices with a printer be seen as hosting an industrial manufacturing process even if the devices are manufactured and used only within that health institution? How should manufacturers of these 3D printed devices, which are not made industrially, but instead go through a custom-made or in-house route, ensure the quality of their products and regulatory compliance for the EU market at present?

2.2. Intellectual property rights

Advances in 3D bio-printing may lead to questions about the ownership of devices and biomaterials implanted in patient's bodies, the patentability of the techniques, and regarding novel biological materials, which differ substantially from 'natural' biomaterials. Article 6(2) of the Biotech Directive states that 'an element isolated from the human body or produced by means of a technical process may be considered as patentable, even if identical to a natural element.' The territorial nature of copyright law, coupled with the exterritorial nature of online platforms and CAD files raise questions about whether these files require copyright protection and can themselves qualify as a copyrightable work fixed in a tangible medium of expression.

One of the main challenges in this field relates to the applicability of the morality clauses enshrined in the European Patent Convention and national patent laws to bar particular patent applications covering bio-printing technology based on the derivation and production of extracellular matrix materials (ECM) and cells. The morality exclusion (53(a) of the European Patent Convention) applies, if human embryonic stem cells are used in bio-printing, based on dignity and identity issues, however this is not the case if stem cells are used for therapeutic purposes (known as the medical treatment exemption). As a result, 3D products/processes must pass the 'morality acceptability test' in order to become patentable.

Focusing on design, is it possible to differentiate between 3D Computer-aided design (CAD) files and 3D replicas? Could the creation of the 3D CAD file replicating a third party design be considered as an infringement of design rights? Additionally, the dissemination of the file might be considered a contributory infringement of the IP rights involved and the creation, dissemination and offering to the public of the 3D replica risks being considered an infringement of design rights, except in the case of private and non-commercial use, experimental use, and in citations or educational uses. In such scenarios, end users risk liability as direct infringers, while the sellers and manufacturers of 3D printers might be exposed to contributory liability, creating a scenario similar to the existing situation in relation to P2P platforms. However, 3D printing might lead to more than the breach of design rights. CADs and replicas might also be protected under copyright, trademark and patent law. A practical problem for regulation may be the sharing of CAD files online and safeguards allowing 3D printers to use authorised CAD files only.

The EU legislator will soon encounter the following questions: Is the existing IP law sufficient to effectively protect both 3D files and those using 3D printing technologies for non-commercial purposes? Who owns an object when it is first conceived by one individual, digitally modelled by another, and printed by a third? Can the person who designed the work and the person who digitally modelled it be considered co-authors of a collaborative work under copyright law? Is biological matter patentable based on the criterion that it is markedly different from the natural version? Is a biotechnological product produced by bio-AM technology also patentable due to the human organism exception, as the ability to produce living tissues or organs with bio-AM blurs the line between the living and the non-living? Should bio-printers be categorised as machines used for a medical purpose, and thus a patentable entity, or non-patentable medical techniques involving direct printing onto or into the body, thereby excluding patenting through the legal 'medical treatment exception'?

2.3. Data protection aspects

An issue that is addressed rather rarely is that CADs and replicas might contain personal data, whereas there is also a pressing need to deal with the massive amounts of data produced by and retained for 3D printing operations. 3D printers store confidential and personally identifiable information on patients, such as schematics, customer configurations and system logs. The loss of that data can compromise trade secrets and intellectual property protection. Medical 3D printing requires the processing of personal data and is therefore subject to the privacy protection offered by the General Data Protection Regulation (GDPR). Personal (health) data might be collected, stored and used in the frame of the manufacturing chain, whereas customisation might link a product to an individual person. The processing of the patient's data for 3D printing purposes is justified according to the GDPR, even without patient consent, as long as the 3D printing is required for the diagnosis or treatment of the patient or for health insurance or legal insurance purposes. Processing for other 3D purposes will normally require the patient's consent. The hospital will generally qualify as the data controller who is responsible for meeting most of the GDPR requirements.

Under the provisions of the GDPR, the hospital and the manufacturer must enter into a processing agreement, which must contain certain provisions concerning the respective responsibilities of both parties. EU law recognises the right to informed consent, but does not provide clear guidance on how to implement this right with regard to innovative devices or techniques such as 3D printing medical devices. Only a licensed person is allowed to remove a living person's transplantable material. Such removal would need to be non-commercial. A fully informed consent process is expected to 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.

The patient is entitled to certain information regarding the data processing. The further processing of the patient's data for other purposes than 3D printing medical devices (especially scientific, marketing and insurance purposes) is also subject to the protection offered by the GDPR. This means that 3D printing does not create an additional privacy hazard in case of further processing of the patient data collected for 3D printing purposes. A national public supervisory authority must supervise the data processing for 3D printing purposes. The transfer of the patient's data to a third country outside the EU (e.g. to 3D printing facilities abroad) normally requires that this country ensures an adequate level of data protection.

The assurance of such adequate protection levels is however not required in some well-defined cases (e.g. patient consent, protection of the patient's vital interests). The GDPR does not make any fundamental changes with regard to either the qualification of patient data collected for 3D printing purposes as personal data, or with regard to the qualification of the hospital as the data controller (and the outsource manufacturer as data processor). The GDPR strengthens the current processing requirements for (health related) personal data and also adds several new requirements (e.g. for 'profiling', a form of data processing that might also take place with regard to the 3D printing of medical devices). In general, this will lead to better protection of the data subject (i.e. the patient), but also to a more expensive and administrative burdensome data protection regime for the hospital controllers and even the outsourced manufacturer processors.

Based on this analysis, a series of questions arises: do hospitals require patients to give privacy consent for the 3D printing of their organs? What happens to that 3D-printed organ after the test surgery? It might be used for research, but might possibly be made available to third parties that through the information contained therein (e.g. the type of disease affecting the patient) might perform direct marketing activities to the third party's benefit, or even change insurance policy premiums.

2.4. Liability

In the context of 3D printing, primary (or 'direct') liability arises when a party is deemed directly responsible for legal harm to another. Those liable are persons who upload infringing designs to 3D

printing design websites for sale, download and print infringing materials from such sites for public use, or traffic in infringing goods. However, the close involvement of patients in the frame of 3D manufacturing, and the fact that the customer is the actual manufacturer, means there is a wide range of different players (owner of the printer, the manufacturer/supplier of the printer and the person that actually created and/or used an untested product), which may lead to potentially overlapping liability responsibilities and the associated regulatory challenges. Additional risks related to 3D printed products include the acquisition and transfer of personal data, as well as the liability of designer and software engineers.

The Product Liability Directive requires the enforcement of strict liability on producers when their products are defective and cause personal injury. This 'strict liability' applies only to products which have been industrially produced, reinstating the relevance of the custom-made vs customisable standard dilemma for qualifying 3D printed devices. The dilemma can have real consequences for the applicable liability regime. The applicability of the Product Liability regime on custom-made devices also extends to medical devices, given that the liability requirement of the Medical Device Regulation (Article 10 (16)) makes no exemptions for manufacturers of custom-made devices.

The producer is liable for damage caused by defect in the product. All producers involved in the production process and all actors in the supply chain can be liable. The producer can be the producer or supplier of the 3D printer, components thereof or the input material, as well as the actor presenting himself as producer. Liability claims require proof by the injured person of (1) damage, (2) defect of the product, (3) causation. A product is defective (Article 6) if it does not provide the safety that a person is entitled to expect.

In general, civil liability is a matter which is not harmonised and is subject to national legislation. EU legislation is limited to more specific rules on issues such as civil liability for defective products. It can be difficult for a victim of a faulty 3D printed object to identify the person responsible. General liability rules can help to identify the manufacturer of the 3D printer, the producer of the software running the 3D printer and the person creating the object. As we are at the beginning of this technological trajectory, caution is required as to whether high-quality 3D products can be made which do not pose a risk to users or consumers. Anticipating problems relating to accident liability or intellectual property infringement will require the adoption of new legislation at EU level or the tailoring of existing laws to specific cases of 3D printing, such as adverse reactions to 3D printed pharmaceuticals and control of customisation and product quality in online platforms that allow sharing of computer aided design (CAD) files.

2.5. Safety issues

Safety constitutes a major regulatory challenge in the field of 3D printing. In the domain of bio-printing, safety refers primarily to the risks associated with undertaking medical procedures outside professional medical environments. The side effects of bio-printing have rarely been addressed, including questions such as biomaterials degradation and tissue integration, biocompatibility, and continuous tissue synthesis during material degradation. In the frame of 3D bio-printing, the DIY body modification community performs medical and non-medical (lifestyle) interventions in non-medical settings. The intended implantation of processed living cells into the human body bears various risks for patients' health. New players, such as DIY communities, and new producers, such as hospitals in a decentralised medical economy, raise challenges with regard to oversight of regulations. Safety and health is one of the very first concerns surrounding 3D bio-printing, given the spread of DIY practices in this domain. In any case, consideration is due regarding how standards can be maintained if advanced 3D bio-printing techniques are more readily available for use outside traditional professional environments. Safety issues include sources of biomaterials, unhealthy donors, implant efficacy, and post-transplant infections. 3D bio-printing remains an untested clinical paradigm and is based on the use of living cells placed into a human body; risks include teratoma and cancer, dislodgement and migration of implanted material.

Several bio-AM applications are entering the clinical trial phase, thereby also creating issues regarding safety testing in humans for disease modelling or testing of pharmaceuticals (e.g. 3D printed ovaria and life size printing of cartilage, bone, ear, muscle tissues, and biocompatible polymers). Other important safety questions relate to the printing materials themselves and the actual printing process. The use of novel polymers, sometimes mixed with nanoparticles, poses long term risks for implants and requires post-marketing surveillance and registries. The increased level of customisation and potential for more decentralisation infrastructure may make it more difficult for consumers and authorities to verify the safety of products. Higher safety standards apply for medical products other than consumer goods, and rules also govern the use of living tissues in laboratories. Such standards present barriers to personalised 3D printed medical devices reaching the market. While these standards could change to support the development of 'mass customisation' for all kinds of medical devices, the changes will continue to prioritise patient safety and affect how a 3D printing infrastructure could emerge within the medical sector. For example, high costs for expertise and facilities could discourage decentralisation.

To ensure the quality and safety of cell and tissue material used in bio-printing, the early stage of donation, procurement, and testing of tissue and cells is governed by the EU Tissues and Cells Directive (EUTCD) 2004/23). A crucial question for product validation and release is how much testing is required when products are both patient-matched (and thus 'batches of one') and potentially made on demand. Testing of the finished product, especially when it is completed *in vivo* after being implanted into the patient, is unlikely. Besides the use of (stem-) cells from patients, cells derived from other human beings bear particular issues in the form of safety risks, including the unintended transfer of disease through implanting tissues or organs printed with those cells. It remains unclear whether bio-AM applications can be assessed similarly to existing products and services, or if they require a completely new validation and testing framework.

The location of manufacture matters in terms when establishing the compatibility of a 3D printing material with biological materials and the printing process. A laboratory with controlled conditions and safety standards or a production plant with quality assurance practices in place (GMP) differs from development and production at home. Cells and living tissues should be handled under strict safety procedures as in laboratories, to prevent distribution of e.g. blood-borne diseases when patient material is used in manufacturing. Furthermore, 3D printing will make it possible to manufacture devices and products in a decentralised way. This technological narrative departs from the underlying assumption of the existing EU product safety system of rules that depends on centralised manufacturing and raises safety questions. One critical question is whether users can judge the safety of products by themselves, a requirement not previously needed with centralised production. For the time being, a significant amount of 3D printing is experimental in nature, and the communities of users may realise that there is a degree of risk inherent in trying out various designs.

2.6. Security

3D bio-printing also raises potential security issues, not only at the individual level, but also collectively. A major concern that is that the technology might be (mis-)used to improve organs by adding functions or interbreeding human cells with those of animals to give the patient a competitive edge over other individuals. Such performance enhancements could inter alia attract individuals involved in professional sport and the military. The possible dual use of 3D printing technology, e.g. in the case that dangerous viruses are printed could possibly lead to questionable practices and outcomes.

Moreover, 3D printers and the broader 3D printing ecosystem face cybersecurity and privacy challenges with significant legal and business risks that need to be addressed. The nature of 3D printers and increasing reliance on 3D printed objects with a wide array of uses present unique issues that demand careful attention. High-profile failures of 3D printed objects as a result of maliciously introduced defects could result in a loss of public faith in the technology, and significantly impact on the industry at large.

Security and dual-use aspects also need to be considered, since almost any civil technology development can be transferred to military technology development. For example, a minor controversy ensued when blueprints for 3D printing guns at home were freely distributed on the internet. The increased accessibility of 3D bio-printing facilities – in terms of cheaper and more readily availability equipment combined and reduced expertise required to use it – paves the way for the production of biohazards or even bioweapons.

2.7. Socio-ethical considerations

Although bio-printing can avoid ethical dilemmas associated with xenotransplantation (engineering of animal organs for transplantation into humans), our reliance on human (and animal) organ donors and the transparent character of clinical organ transplantation, it raises a series of important ethical questions regarding the use of cell source for bio-printing and the accessibility and affordability of the latter. The use of Human Embryonic Stem Cells (HESCs) as bio-ink material is an ethically questionable practice that calls for an extensive debate in the frame of 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.

Fabricating functional organs in a bio-printing process is a costly procedure that is available mostly to those who can afford such treatment. The high cost of the bio-printing manufacturing process and the required production capacity raise social and distributive justice questions and issues of fair or equal access given also the highly individualised character of the products. The challenge here is to safeguard that innovation paths and regulation result in affordable, accessible and societally responsible bio-AM applications that improve public health and that will not exert pressure on the job market prospects of dental lab technicians.

3D bio-printing raises also questions about the boundaries between therapy and human enhancement or other body modification techniques, given its capacity to enhance individual human performance. The potential for distributed and local production of some bio-AM applications also implies increased responsibility for users, not only regarding the safety and quality standards in production, but also concerning individual behaviour. Moreover, a technology that allows every part of the human organism to be reprinted, may also be used to print a copy of an entire human being. Given the gradual phasing and even ban on cosmetic testing, bio-printing may contribute to a reduction in animal experiments, e.g. by fabricating physiologically functional tissues in limited sizes to be used for medical research and toxicology assays instead of animal subjects.

3. Conclusions

Three-dimensional (3D) bio-printing poses a series of challenges to the existing legal regime across a wide range of issues such as bioethics, safety, regenerative medicine, tissue engineering, and intellectual property (IP). The topics include issues arising from customisation, which will likely challenge the definitions of 'manufacturer' and 'placed on the market' in the regulatory sphere. These range from the fundamental philosophical and bioethical issues to practical risk, biosafety and security concerns. Concerns also exist that the current regulatory framework is ill-equipped to mitigate risks to patients, and to meet requirements for health care providers and manufacturers. Despite the fact that several applications of 3D bio-printing have been commercialised, the EU has not yet developed any strategy towards 3D bio-printing.

3D bio-printing presents the recurrent risks and challenges arising from implantable medical devices, cell therapy, stem cell therapy, and organ transplantation. However, existing regulatory frameworks do not account, for example, for aspects related to customisation or to differences between products manufactured using 3D printing technology and conventional tissue engineering methods. Current regulatory regimes on cell therapy and stem cell research lack clarity when considering their application to bio-printing regulation. The legal uncertainties of bio-printing are further compounded by the multiple actors involved in the supply and production chain. A re-definition of 'custom-made device'' is needed, as well as clarification of the terms of certification where high-risk 3D printed medical devices are concerned. High-risk custom devices, such as 3D printed implants, can be certified in the same way as low-risk devices that are not made to be hosted under the skin, e.g. glass eyes and prescription lenses. EU authorities do not provide a clear statement on the categorisation of corresponding 3D prints.

Healthcare professionals must communicate all scientific uncertainties related to 3D printing – which is a challenging task in itself, given the lack of harmonised rules on informed consent. Donors should be informed of the current and future use of their cells and tissues. It is suggested that complete details of the composition of a bio-printed product, the implantation process, all conflicts of interest, and all potential outcomes and adverse effects are noted in the consent form. Databases on patients receiving customised organs and tissue are associated with many regulatory issues on data protection. The production of personalised manufactured tissue and organs also calls for an EU-wide infrastructure for storing the records of encrypted and protected files and the design of printers connected to and equipped with a system capable of managing intellectual property rights. Developers and innovators in the field may benefit from clearer guidance on how their products are defined and classified, which would help them to understand which regulations, standards and procedures apply to them. Responding to the legal and socio-ethical challenges mentioned above requires the introduction of technology-specific standards for medical products, given the wide spectrum of this technological trajectory, the heterogeneity of bio-AM applications, and their emerging status.

EU legislators need to begin a debate on the nature and classification of bio-printed organs, and to address the tension between cell/DNA banks and digital databases. Furthermore, there is a need for a discussion about whether enhanced bio-printed organs, as well as crossbred organs, should be added to the catalogue of Article 6 (2) of the Biotech Directive as unethical and un-patentable, to establish a more harmonised approach. A 'portfolio approach' to legal licensing in bio-printing has been suggested, that would place responsibility on companies to share benefits as well as emphasising the key role of publicly funded research. It would be also advisable to distinguish between home printing for private use and printing for commercial use, and between B2B and B2C services. Although general liability rules also apply to 3D printing, a specific liability regime could be envisaged for damage caused by an object created using 3D printing technology, as the decentralised character of 3D bio-printing and the number of stakeholders involved in the process often make it difficult for the victim to identify the person responsible.

4. References

Abbott, Alison. 'Europe Rules against Stem-Cell Patents: Work with Human Embryonic Stem Cells Is 'Contrary to Ethics', (European Law).' Nature 471, no. 7338 (2011): 280.

Ahearn, A. (2016): 'Ethical Dilemmas in Liver Transplant Organ Allocation: Is it Time for a New Mathematical Model?'. *AMA journal of ethics* 18. (2), 126–132.

Bauer, H. K., M. Heller, M. Fink, D. Maresch, J. Gartner, U. M. Gassner, and B. Al-Nawas. 'Social and Legal Frame Conditions for 3d (and) Bioprinting in Medicine.' [In English]. International Journal of Computerized Dentistry 19, no. 4 (2016): 293-99.

Bradshaw, S.; Bowyer, A. & Haufe, P. (2010): 'The intellectual property implications of low-cost 3D printing'. *ScriptEd* 7. (1), 5–31.

Bunzel, B.; Schmidl-Mohl, B.; Grundböck, A. & Wollenek, G. (1992): 'Does changing the heart mean changing personality? A retrospective inquiry on 47 heart transplant patients'. *Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation* 1. (4), 251–256.

Chae, M. P.; Rozen, W. M.; McMenamin, P. G.; Findlay, M. W.; Spychal, R. T. & Hunter-Smith, D. J. (2015): 'Emerging Applications of Bedside 3D Printing in Plastic Surgery'. *Frontiers in Surgery* 2, 25.

Chhaya, M. P.; Poh, P. S. P.; Balmayor, E. R.; van Griensven, M.; Schantz, J.-T. & Hutmacher, D. W. (2015): 'Additive manufacturing in biomedical sciences and the need for definitions and norms'. *Expert Review of Medical Devices* 12, 537–543.

d'Aveni, R. (2015): 'The 3-D printing revolution'. *Harvard Business Review* 93. (5), 40–48.

Despeisse, M.; Baumers, M.; Brown, P.; Charnley, F.; Ford, S. J.; Garmulewicz, A.; Knowles, S.; Minshall, T.H.W.; Mortara, L.; Reed-Tsochas, F. P. & Rowley, J. (2017): 'Unlocking value for a circular economy through 3D printing'. *Technological Forecasting and Social Change* 115, 75–84.

Di Prima, Matthew at al. 'Additively Manufactured Medical Products - the FDA Perspective.' 3D Printing in Medicine 2:1 (2016).

Dolinsky, Kyle. 'Cad's Cradle: Untangling Copyrightability, Derivative Works, and Fair Use of 3d Printing.' (2013): 92.

Dufner, A. & Harris, J. (2015): 'Trust and altruism—organ distribution scandals: do they provide good reasons to refuse posthumous donation?'. *The Journal of medicine and philosophy* 40. (3), 328–341.

Ebrahim, T. Y. (2017): '3D Bioprinting Patentable Subject Matter Boundaries'. *Seattle UL Rev* 41, 1.

Ely, S. (2009): 'Personalized medicine'. *Translational Research* 154. (6), 303–308.

Gilbert, F.; O'Connell, C. D.; Mladenovska, T. & Dodds, S. (2017): 'Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine'. *Science and engineering ethics*, 1–19.

Güth, J.-F.; Keul, C.; Stimmelmayr, M.; Beuer, F. & Edelhoff, D. (2013): 'Accuracy of digital models obtained by direct and indirect data capturing'. *Clinical Oral Investigations* 17, 1201–1208.

Haddow, G.; Bruce, A.; Calvert, J.; Harmon, S. H.E. & Marsden, W. (2010): 'Not 'human' enough to be human but not 'animal' enough to be animal – the case of the HFEA, cybrids and xenotransplantation in the UK'. *New Genetics and Society* 29. (1), 3–17.

Harbaugh J T. 'Do you own your 3D bioprinted body? Analyzing property issues at the intersection of digital information and biology'. *Am J Law Med 2015; 41:167–89.*

Hourd, P.; Medcalf, N.; Segal, J. & Williams, D. J. (2015): 'A 3D bioprinting exemplar of the consequences of the regulatory requirements on customized processes'. *Regenerative medicine* 10. (7), 863–883.

Li, P. H., '3D bioprinting technologies: patents, innovation and access'. *Law Innov Technol 2014;6: 282–304. doi:10.5235/17579961.6.2.282*

Li, J.; Hsu, Y.; Luo, E.; Khadka, A. & Hu, J. (2011): 'Computer-Aided Design and Manufacturing and Rapid Prototyped Nanoscale Hydroxyapatite/Polyamide (n-HA/PA) Construction for Condylar Defect Caused by Mandibular Angle Ostectomy'. *Aesthetic Plastic Surgery* 35, 636–640.

Li, J.; Li, P.; Lu, H.; Shen, L.; Tian, W.; Long, J. & Tang, W. (2013): 'Digital Design and Individually Fabricated Titanium Implants for the Reconstruction of Traumatic Zygomatico-Orbital Defects', *Journal of Craniofacial Surgery* 24, 363–368.

Li, P. H. (2014): '3D Bioprinting Technologies'. *Law, Innovation and Technology* 6. (2), 282–304.

Li, P., and A. Faulkner. '3d Bioprinting Regulations: A UK/EU Perspective.' [In English]. European Journal of Risk Regulation 8, no. 2 (Jun 2017): 441-47.

Li, Phoebe and Faulkner, Alex. '3d Bioprinting Regulations: A UK/EU Perspective.' European Journal of Risk Regulation 8, no. 2 (2017): 8.

Mandrycky, C.; Wang, Z.; Kim, K. & Kim, D.-H. (2016): '3D bioprinting for engineering complex tissues'. *Biotechnology advances* 34. (4), 422–434.

Marga, F.; Jakab, K.; Khatiwala, C.; Shepherd, B.; Dorfman, S.; Hubbard, B.; Colbert, S. & Gabor, F. (2012): 'Toward engineering functional organ modules by additive manufacturing'. *Biofabrication* 4, 22001.

Melchels, F. P.W.; Domingos, M. A.N.; Klein, T. J.; Malda, J.; Bartolo, P. J. & Hutmacher, D. W. (2012): 'Additive manufacturing of tissues and organs'. *Progress in Polymer Science* 37. (8), 1079–1104.

Mironov, V.; Boland, T.; Trusk, T.; Forgacs, G. & Markwald, R. R. (2003): 'Organ printing'. *Trends in Biotechnology* 21. (4), 157–161.

Mota, C.; Puppi, D.; Chiellini, F. & Chiellini, E. (2015): 'Additive manufacturing techniques for the production of tissue engineering constructs'. *Journal of Tissue Engineering and Regenerative Medicine* 9, 174–190.

Murphy, S. V. & Atala, A. (2014): '3D bioprinting of tissues and organs'. *Nature biotechnology* 32. (8), 773–785.

Neely, E. L. (2016): 'The Risks of Revolution: Ethical Dilemmas in 3D Printing from a US Perspective'. *Science and engineering ethics* 22. (5), 1285–1297.

Ng, P.; Lui, L.; Lee, V. S.P.; Tan, K. C.; Tay, E. H. & Goh, J. C. (eds.) (2002): *Rapid manufacturing machine (RMM) for prosthetic socket fabrication*.

Nissan, A. M. 'Regulating the Three-Dimensional Future: How the FDA Should Structure Regulatory Mechanism for Additive Manufacturing (3d Printing).' (2014).

Norman, J.; Madurawe, R. D.; Moore, C. M.V.; Khan, M. A. & Khairuzzaman, A. (2017): 'A new chapter in pharmaceutical manufacturing: 3D-printed drug products'. *Editor's Collection 2016Editor's Collection* 108, 39–50.

Otto, I. A., C. C. Breugem, J. Malda, and A. L. Bredenoord. 'Ethical Considerations in the Translation of Regenerative Biofabrication Technologies into Clinic and Society.' [In English]. Biofabrication 8, no. 4 (Dec 2016): 7.

Pink, J. (2015): 'Risks of Additive Manufacturing: a Product Safety Perspective'. https://www.mddionline.com/risks-additive-manufacturing-product-safety-perspective.

Scheper-Hughes, N. (2000): 'The Global Traffic in Human Organs'. *Current anthropology* 41. (2), 191–224.

— (2003): 'Keeping an eye on the global traffic in human organs'. *Lancet* 361. (9369), 1645–1648.

Skene, L. 'Stem Cells and Translational Medicine: Ethics, Law, and Policy.' Frontiers in Pluripotent Stem Cells Research and Therapeutic Potentials: Bench-to-Bedside (2012): 83-94.

Tran, Jasper L. 'The Law and 3d Printing.' J. Information Technology and Privacy Law 31, no. 4 (2015).

Tran, Jasper L, 'Press Clause and 3d Printing.' Northwestern J of Technology and Intellectual Property

14, no. 1 (2016).

Tran, Jasper L, 'To Bioprint or Not.' North Carolina J of Law & Technology 17, no. 1 (2015).

Tran, Jasper L. 'To Bioprint or Not to Bioprint.' North Carolina Journal of law & Technology 17, no. 1 (October 2015 2015).

van Noort, R. (2012): 'The future of dental devices is digital'. *Dental Materials* 28, 3–12.

Varkey M, Atala A, *Organ bioprinting: a closer look at ethics and policies. Wake Forest J Law Policy 2015; 5:75–298.*

Vermeulen, N.; Haddow, G.; Seymour, T.; Faulkner-Jones, A. & Shu, W. (2017): '3D bioprint me: a socioethical view of bioprinting human organs and tissues'. *J Med Ethics*.

Vermeulen, Niki et al. '3d Bioprint Me: A Socioethical View of Bioprinting Human Organs and Tissues.' J med Ethics 43 (2017): 7.

Vijayavenkataraman S, Lu W F, Fuh J Y H, *3D bioprinting – an Ethical, Legal and Social Aspects (ELSA) framework. Bioprinting 2016; 1–2:11–21.* doi:10.1016/j.bprint.2016.08.001

Vijayavenkataraman, S. 'A Perspective on Bioprinting Ethics.' Artificial Organs 40, no. 11 (Nov 2016): 1033-38.

Wohlers, T. T.; Campbell, R. I. & Caffrey, T. (2016): *Wohlers report 2016. 3D printing and additive manufacturing state of the industry: annual worldwide progress report*. Fort Collins, Colo., Fort Collins, Colo.: Wohlers Associates.

Yoo, S.-S. (2015): '3D-printed biological organs'. *Expert opinion on therapeutic patents* 25. (5), 507–511.

Yoo, S. S. '3d-Printed Biological Organs: Medical Potential and Patenting Opportunity.' [In English]. Expert Opinion on Therapeutic Patents 25, no. 5 (May 2015): 507-11.

The aim of this In-depth Analysis is to illustrate the different ways in which the current EU legislative framework may be affected by the emergence of 3D printing for medical and enhancement purposes and the respective technological trends. Building upon the STOA study, 'Additive bio-manufacturing: 3D printing for medical recovery and human enhancement', it analyses the issues that might arise, identifying the European Parliament committees concerned and the legislative acts that might need to be revisited, especially in view of the recently adopted report and resolution on 'Three-dimensional printing, a challenge in the fields of intellectual property rights and civil liability' (2017/2007(INI)). This analysis also provides a series of overarching recommendations that EU actors may wish to take into account when dealing with 3D bio-printing, resulting from an examination of the multiple ethical and legal challenges associated with this emerging technology, as well as a scan of current legislation in a wide range of areas of EU policy-making.

This is a publication of the Scientific Foresight Unit (STOA)
EPRS | European Parliamentary Research Service, European Parliament

PE 614.571
ISBN 978-92-846-3148-3
doi: 10.2861/923327
QA-01-18-636-EN-N