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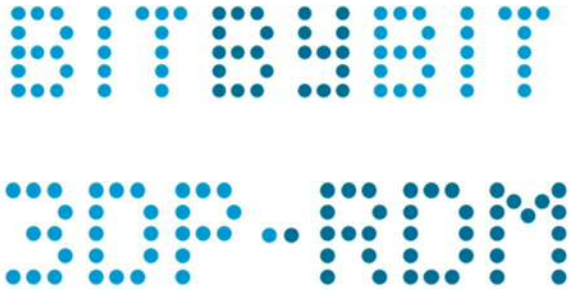

EPSRC
Engineering and Physical Sciences Research Council

Mass customisation governance: regulation, liability, and intellectual property of re-distributed manufacturing in 3D printing

Project Report

ABSTRACT

The feasibility study assesses the impacts of existing legal regimes on re-distributed manufacturing (RDM) in 3D printing (3DP). It investigates the viability of an embedded watermarking system into mass customisation governance of RDM as part of the potential impact of the three most important regimes on 3DP - regulation, liability, and intellectual property (IP) - in order to secure safety, quality control, surveillance, and traceability.

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CHAPTER 1. INTRODUCTION

'Advanced Therapy Medicinal Products' (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. Most bioprinted medical products will be ATMPs. Due to the novelty, complexity and technical specificity of ATMPs, they present a wide range of quality challenges, from a manufacturing perspective, which differ from those of medical devices and synthetic or non-living biological therapies.

The introduction of decentralized computer-aided manufacturing (CAM) further compounds the thorny issues of risk management in the 'chain of custody' and the 'quality of materials', due to the involvement of different stakeholders such as CAD designers, in the production chain. It begs the question as to how big the footprint of bioprinting should be, and also what the optimal product cycle ought to be? In this project we aim to delineate who is responsible for what, clarifying the changing faces of 'products' and 'manufacturers' in the legal sphere, challenged by digital manufacturing in 3D bioprinting.

We can distinguish broadly between two organizational modes for bioprinting. In centralised bioprinting patients would be diagnosed in distributed (geographically dispersed) hospitals where data is scanned and sent to one central manufacturing site. Products are manufactured and then shipped back to the hospitals.[1] The storage of the data could be at external printing labs, hosted sites, or sent outside of the EU. Alternatively, decentralized or 'Redistributed Manufacturing' (RDM) of bioprinting refers to decentralized business models that place bioprinters in the hospitals. Associated benefits include reduced product lead time, and the avoidance both of transporting living cells and removal of patient data from the hospital.

Centralised bioprinting would require additional measures in data protection specifically in relation to transfer of patients' data between the hospital and the manufacturing site. RDM bioprinting, on the other hand, would need to focus more on the individual hospital's certification of facilities (CE marking, Quality System and ISO requirements), documentation, and delivery systems. The selection of viable business models would depend on technical and economic feasibility studies based on cost-benefit analyses.

[1] 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 02 January 2017.

For the purpose of safeguarding quality and traceability of products, in Chapter 5 we examine the role of watermarking as a technological tool to be used in decentralized 3D bioprinting manufacturing as a means of attributing 'Copyright Management Information (CMI)'.[2]

The aim of the report is to identify the future regulatory directions for better facilitating bioprinting as well as to develop bioprinters to best fit within current regulations. Chapter 2 will introduce the state-of-the-art re-distributed manufacturing in 3D bioprinting by revisiting the cases of nose and ear reconstruction. Chapter 3 will map the relevant medical products, laws, and regulations in the EU/UK. Chapter 4 discusses the management of legal duties and liabilities of re-distributed manufacturing of 3D bioprinting. In Chapter 5 we evaluate the effectiveness and limitations of using watermarking in the production chain for the purposes of safeguarding the origin and quality of materials, of accountability, of traceability of products, and of intellectual property protection. We conclude in Chapter 6 with preliminary remarks and future work.

CHAPTER 2. RE-DISTRIBUTED MANUFACTURING OF 3D BIOPRINTING: THE TECHNOLOGIES AND CASE SCENARIOS

Three-dimensional printing (3DP) is a technology that enables agile and responsive manufacturing to take place at locations closer to the patient than would otherwise be possible. Products that may be manufactured range from medical devices - often with customisable and personalisable features - through pharmaceutical dosage forms such as compartmentalised oral formulations to advanced therapeutic medicinal products (ATMPs). The latter category provides a useful illustration of the challenges to current manufacturing and supply paradigms.

A. Manufacturing process regulation

When the first chemical processes were transferred to large-scale production in the 19th century the innovators who wished to create profitable, effective manufacturing processes discovered that manufacturing on a large scale was accompanied by a change in the features that exerted the most influence over product properties. These features had been overlooked in small-scale operations because they were so easily controlled by human operators working with limited volumes of material, so their significance did not come to the fore. At large scale the operational challenges of moving, heating, cooling, mixing and separating reagents and

[2] For more information see Chapter 3.

products became more challenging, and this in turn made the control of critical temperatures, volumes and timing much more challenging. The discipline of chemical engineering emerged to meet this challenge and with it the specific study of heat and mass-transfer operations in order to realistically predict the behaviour of practical manufacturing steps with confidence. Over time came a realization of certain recurring scenarios, and these groupings of features led to the definition of 'unit operations'. Unit operations provide a convenient shorthand for the description and communication of process designs.

Bioprinting is another example of a technology that presents fresh challenges with timing, materials movement and temperature control. Some of these challenges will be common to many out-scaled manufacturing operations that involve materials and living cells. The scale and technical scenarios differ markedly from the up-scaling of chemical processes. Nevertheless these scenarios will be repeated from one manufacturing design to another.[3]

The current regulations have emerged from the evolving context of manufacturing for medical devices, herbal products and pharmaceuticals. Each of these categories assume that the processing operations are defined early in the manufacturing research cycle and that the unit operations deliver products with single-value characteristics. The new unit operations described above allow for different parameters from lot-to-lot and, therefore, require a modification of the control strategy (described in the Appendix to ICH Q8 (R2)),[4] i.e. an enhanced Quality by Design approach in which the design space allows for degrees of customization within control limits that are related to cell characteristics and to the product critical dimensions.

B. The distinction between transplants and ATMPs

The alginates and fibrin materials tend to have low structural resilience and are assimilated fairly quickly by the body. Polycaprolactone lasts much longer. The well-used biodegradable polymers - poly(glycolic acid), poly(lactic acid), and their copolymers (PLG, PLA and PLGA respectively) - are tricky to use in bioprinting because aggressive, toxic solvents are needed.

[3] To provide such a vocabulary is beyond the scope of this article. However, it is reasonable to assume that unit operations such as 'controlled bioextrusion' (cells plus carrier passing through a narrow nozzle in such a way as to maintain a window of fluid shear stress, pressure drop and temperature gradient) and '3D hold step' (construct assembly for a fixed duration from first to last moment of the 3D printing whose pace, humidity, aeration and temperature is determined by the relative rates of cell nutrition, drying and cooling) will be early additions to the engineering vocabulary.

[4] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 'Pharmaceutical development Q8(R2)' (ICH Harmonised Tripartite Guideline) [2009] < www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf> accessed 19 December 2016.

Nevertheless we can imagine them being used to make sheets that are then added together to make constructs. These degrade in days (PGA), weeks (PLA) and a spectrum in-between (PLGA, depending on ratios), and release acid as they do so which in turn accelerates the degradation so the degraded products cannot exit the construct e.g. in the blood supply an exponential degradation pathway is followed that resembles catastrophic failure days after implantation. Non-degradables such as acrylates, methacryates and vinylpyrrolidone derivatives are chemically crosslinked during manufacture and remain structurally resilient for a long time.

The main tools for structural tissue will be MRI and CAT or PET scans. Angiography will show the extent to which the blood supply has integrated with the implant. Simple dent compression tests could be done to establish the resilience of the tissue to compression.

The difference is between 'minimal manipulation for homologous use' (i.e. the same purpose as in nature and the cells have not been grown up in number) which makes it a tissue and more than minimal manipulation and/or for non-homologous use (tissue engineering). In the US these are the '351' and '361' products in those sections of the Public Health Service Act 1944 (42 USC 264).

The nature of a bioprinted product is that it has the characteristics of an ATMP and some similarity to an ATMP-device combination product because it has characteristics of a device (implant to support the body) but operates primarily by means of its living characteristics. Therefore, although the current regulatory difficulties relate to the issues of specification,[5] it would at least have to be approved via the route of a medicinal product and as an ATMP including proof-of-concept, pre-clinical efficacy and safety, the usual clinical phases and post-market surveillance. In addition, there would need to be a robust 'comparability protocol' in place early in development that prescribed the (hopefully concise and limited) bridging studies that will be needed in order to approve each new bioprinting facility or site. The divergence from current practice is in two areas: a) economical qualification of each new bioprinting machine and/or site, and b) the unusually high burden of work necessary to prove the specification, and, in particular, to identify and justify the Target Quality Product Profile.

C. Work to date

Two studies in particular have been evaluated for the present project. They have some characteristics in common. The first is a feasibility study conducted as part of the Re-

[5] See Chapter 3.

distributed Manufacturing in Healthcare Network (RiHN) activity.[6] This was one of five such studies funded by the EPSRC. The topic under consideration was the manufacture of a construct to replace partial or total loss of the nose in patients who had suffered trauma or who had lost tissue due to cancer excision. The study was conducted at the University of Nottingham. The second study was conducted at a series of clinical research centres in the Netherlands[7] and addressed reconstruction of the ear. In both cases a combination of materials printing and introduction of cells made it possible in some versions of the product to provide a permanent implant to be integrated into the patient's body. At the time of writing the regulatory status of the products that are to be made by co-printing of cells and scaffold materials is unclear, but it is reasonable to suppose that the requirements will either be, or will closely parallel, the requirements for a medical device-ATMP combination product with ATMP lead characteristics.[8]

In both cases the advantages of the co-printing of the material and the cells close to the clinic arise from the avoidance of a potential cryopreservation step (which, though achievable, would introduce an unnecessary source of variation), and from the ability to coordinate manufacture with application, enabling a surgeon to use the product straight from the manufacturing bioprinter without the introduction of a 'hold' step during which the cells may diverge from the desired behaviour.

The manufacture of 3D products such as these brings with it several technical hurdles that must be carefully managed to provide goods that are 'comparable',[9] in the regulatory sense, from 'site to site' and from 'batch to batch'. These have been reported in the Feasibility Study Management Report. In the present report attention has been restricted to the legal and intellectual property aspects. The ready availability of the 3D printers means that superficially similar products could be made and similar procedures could be carried out at premises (for example, in areas where there is currently medical tourism for stem cell treatments) that are not subject to GMP compliance oversight by a regulatory authority (and hence have a competitive advantage compared with those sites that are compliant).[10] Technical as well as

[6] 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 02 January 2017.

[7] DO Visscher, EJ Bos, M Peeters, NV Kuzmin, ML Groot, MN Helder, and PPM van Zuijlen, 'Cartilage tissue engineering: Preventing tissue scaffold contraction using a 3D-printed polymeric cage' [2016] 22 Tissue Engineering Part C 6, 573-584.

[8] See Chapter 3.

[9] U.S. Department of Health and Human Services, Food and Drug Administration 'Guidance for Industry: Comparability Protocols, Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information.' [2016] Draft revision 1/April.

[10] The site may be subject to Good Manufacturing Practice (GMP) regulatory oversight, but the product will not have a Marketing Authorisation or equivalent for the product for that territory. That

legal restrictions are needed to protect patients and legitimate innovators alike from such risks.

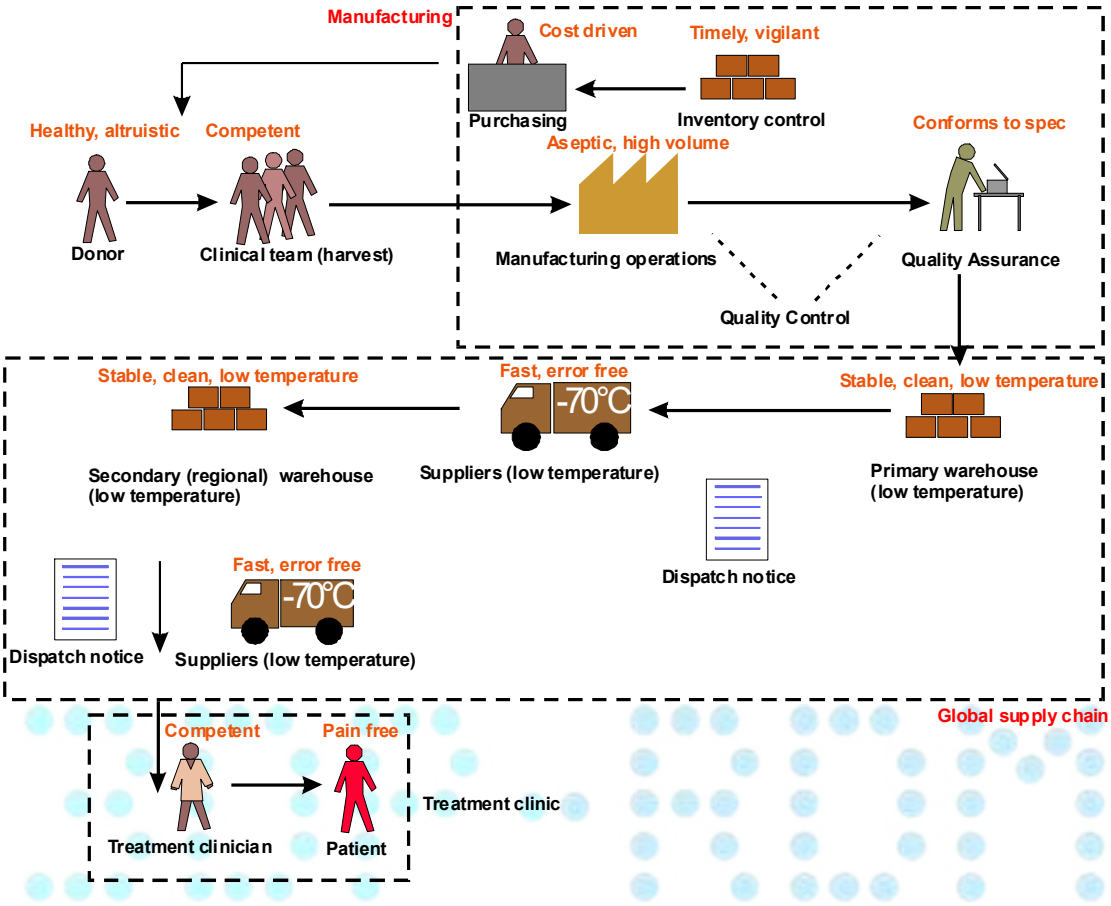

Fig 2. The supply chain of bioprinting products[11]

CHAPTER 3. ATMPS AND REGENERATIVE MEDICINE PRODUCT REGULATION

A wide range of current medical product regulations is applicable to regenerative medicine products broadly, and ATMPs more specifically, in the UK and EU regulatory environments. 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

may not be a problem if the production and administration is subject to an exemption, but the lower level of control and the authority of a healthcare professional may be compromised by the profit motive.

[11] N Medcalf, 'A new business model for cell-based therapeutics' (PhD thesis, NUI Galway, 2011).

interpretations.[12] Our initial view is that the main novelty lies in the processes of manufacture rather than in the product itself.[13]

A. The regulatory regimes

The four main regulatory regimes covering regenerative medicine products applicable in the UK are regulations for: pharmaceuticals, medical devices, ATMPs, and the 'European Union Tissues and Cells Directives' (EUTCD). The regulations for pharmaceuticals, medical devices and ATMPs are designed, with certain important exemptions, to cover commodities which can be put on the market. The so-called 'EUTCD' cover a range of processes from sourcing of human material to storage and processes such as cleaning etc.[14] The latter is administered in the UK by the Human Tissue Authority, and the former three areas by the Medicine & Healthcare products Regulatory Agency (MHRA). The following explanations and observations are key to understanding the potential place of bioprinted products or therapies in the existing regulatory frameworks directly applicable in the UK.

The ATMP Regulation 2007 covers gene therapy medicinal products, cell therapy medicinal products, tissue engineered products, and combinations of one of the three with a medical device component.[15] At the time of writing, the regulation is implemented at EU level through the European Medicine Agency, and especially its Committee for Advanced Therapies which advises the central medicine authorizing committee. The UK regulator, the MHRA, implements relevant regulations in the UK and makes notable interpretations of flexible provisions (such as the ATMP Hospital Exemption).

It is currently unclear whether bioprinters as manufacturing equipment will be regulated as medical devices (with a direct intervention in the human body) or as machinery, currently

[12] Possibly the main novelty is the repeated production of individualised products, using the same bioprinting equipment, which is not quite the same process as envisaged in 'Specials' or the ATMP Regulation hospital expemption or medical device in-house exemption. The characteristics of the process will always be the same. Producers (however defined) 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'?"

[13] The process introduces the potential for unwanted variability in addition to the customisation.

[14] 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 [2004c] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0023&rid=1> accessed 23 August 2016.

[15] 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 [2007] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&rid=1> accessed 23 August 2016.

under the Machinery Directive in the EU.[16] Different testing and data requirements would follow depending on the classification.

More commonly, and in the two case studies presented in this report, the 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, such as a hydrogel carrier for the viable cells (referred to as 'co-printing' in the discussion above). These are designations that the European Medicines Agency's Committee for Advanced Therapies adjudicates on.[17]

B. The Hospital Exemption (HE)

The single most controversial feature of the ATMP Regulation has been the 'hospital exemption'.[18] 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, compliance with an individual medical prescription for a custom-made product for an individual patient.

It is known that few products have been authorized by MHRA 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.[19] Hence, a main area of regulation to be resolved is whether

[16] Council Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery, and amending Directive 95/16/EC (recast) [2006] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006L0042&from=en> accessed 19 December 2016.

[17] PC Hourd, 'A 3D bioprinting exemplar of the consequences of the regulatory requirements on customised processes' [2015] 10 Regenerative Medicine 7, 863-883.

[18] See K Alheit, 'The applicability of the EU Product Liability Directive to software' [2001] 34 The Comparative and International Law Journal of Southern Africa 2, 188-209; MHRA, 'Guidance on legislation: guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC' (MHRA: London, 2013) <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/376918/Guidance_on_the_In_Vitro_Diagnostic_Medical_Devices_Directive.pdf> accessed 01 September 2016; E 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 01 September 2016.

[19] MHRA, 'Guidance on "non routine"'

bioprinted products, repeatedly using the same manufacturing equipment, will be regarded as operating in a routine/industrial, or non-routine/craft-like manner.

In summary, while the current EU ATMP Regulation is the legislative instrument that will be most applicable to bioprinted therapeutic products manufactured at UK facilities (and similar provisions are likely to continue when the UK leaves the EU), a wide range of other regulatory measures will also come into play depending partly upon the processing and material composition of products. And, crucially, there remain regulatory uncertainties as to how 'mass-customised' products can, and should be, classified and regulated.

CHAPTER 4. LIABILITY

A. Liability Management

The traditional model of the relationship between manufacturer and customer has been a simple transaction point in which the customer pays for a manufactured good and, provided that the good is fit for purpose and as described, the responsibilities on both sides are easy to define. With the advent of advanced manufacturing and 3DP the boundaries are less well-defined. The question "where does the manufacturing end" is not easy to answer.

The steps in manufacturing a cell and polymer-printed construct using autologous cells involve initial harvest of cells from the patient tissue (e.g. during wound clean-up), isolation of cells from that tissue, formulation for bioprinting, co-printing of polymer(s) and cells, transfer of the construct to the clinic, removal of construct from the carrier container, preparation of the implant site, final preparation (e.g. by trimming) of the construct, and implantation. Which of these steps constitutes 'manufacture'? At each stage the outcome of the procedure can be adversely affected through the introduction of adventitious microorganisms, contamination, or inappropriate manipulation such as over-trimming or poor temperature control. The liability for successful outcome is therefore **shared** between the staff who carry out the bioprinting and the staff who harvest the tissue and who carry out the implantation.

The point of introduction of a pathogen is particularly difficult to prove retrospectively. With the large-scale manufacture of parenteral medicines (such as vaccines in the EU) there is a requirement to retain a portion of the batch in case of the need to re-test and to conduct

<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf> accessed 02 January 2017.

sterility testing on a portion of the batch as part of the release criteria for the product.[20] With individualized complex products this is difficult or impossible given the limited starting materials and the expense and ethical considerations (it may require an additional tissue sample biopsy) involved in making each one. In the event of a patient infection there may be accusations of fault on either side that cannot be substantiated. Liability will be difficult to assign and to police. Two solutions present themselves based on the business model and on technical design.

If the business model is based upon a franchise-style arrangement under which the innovators (a separate legal entity) provide a training package, bioprinting machine (and aseptic enclosure) and the consumables and equipment in order for the clinic to make the products, then the role of the manufacturer of the implants is wholly adopted by the clinic and the goods fall into the category of 'hospital exemptions' (see the above Chapter 3 on medical product regulations), or part of the practice of medicine rather than a product governed by a Marketing Authorization.[21] The 'franchise-giver' then realizes their value by enabling the activity rather than by selling the products.

The technical design approach involves manufacturing the good as a 'product', subject to a Marketing Authorization, including in the design of the carrier kit an arrangement whereby the user or clinician returns part or all of the aseptic medium in which the good was supplied. The returned sample is then tested for infection before discarding, thus providing evidence of asepsis up to the point of use. This arrangement provides assurance for the manufacturer and for the patient. It need hardly be added that, in the event that an infection is detected, there should be a legal duty to inform the patient and the clinic. The decision whether to effect a removal of the product would be taken based upon a risk to benefit assessment in which the health of the patient, the nature of the infection and the status of the patient immune system

[20] The requirement to retain a sample for at least one year. See Commission, 'The rules governing medicinal products in the European Union. Volume 4 EU guidelines to good manufacturing practice medicinal products for human and veterinary use: Reference and retention samples' [2005] 4 EudraLex Annex 19 <https://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/2005_12_14_annex19_en.pdf> accessed 19 December 2016.

[21] There is concern that the 'Hospital Exemption' (HE) can be misused *i.e.* by producers repeatedly producing 'customised' products using the 'same' production set-up. In the UK MHRA say they monitor numbers of HE'd procedures, see MHRA, 'Regulation (EC) No 1394/2007 on advanced therapy medicinal products ("The ATMP Regulation"): Guidance on the UK's arrangements under the Hospital Exemption Scheme' <www.gov.uk/government/uploads/system/uploads/attachment_data/file/397738/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf> accessed 02 January 2017. This surely gets to the heart of the 'customised'/'mass' conundrum. Some operations are pushing the boundaries of the definition and the Competent Authorities may have to take action soon to contain it.

would be factors.

In order to manage the risks associated with redistributive manufacturing (RDM) of bioprinting and to attribute liability, we are focusing on the discussions on the 'Chain of Custody' and the 'Quality of Materials'. 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 the bioprinting and materials.[22]

Questions in relation to liability issues that arise here are: what is a 'product'? Is CAD blueprint and computer code to be considered a 'product'? What is a 'defect'? Who is the producer? Is a hospital that implants 3D bioprinted products regarded as a 'seller' of products? What are the attributable liabilities in the chain of custody? Is the manufacturer of the 3D bioprinter bearing any liability? Are medical software and CAD design files to be considered 'products' in the context of product liability legislation?

The 3D bioprinting process involves collection and processing of personal data concerning health on many levels: data from hospital electronic health records, generation of patient-related data for end product, data in CAD files describing the end product, etc. These all challenge the existing regime for patient data protection as follows: customization and traceability for product safety make patients identifiable, anonymity difficult, and data can be breached and stolen. The controller of the data has regulatory burden. An agreement on who can access the data needs to be established.[23]

The following section explores the possibilities of pursuing product liability claims in relation to receiving treatment via 3D bioprinting. The assumption remains that the usual avenue of 'medical negligence' claims, where a patient has suffered injury arising from clinical negligence, is still applicable. The scope of this work will primarily focus on delineating the scope of 'product' liability in 3D bioprinting.

[22] Human errors could be due to temperature control enclosure, print head nozzle obstruction, and location; see K Paroha, '3D printed products, product liability and insurance implications' (*Kennedys* 2 June 2014) available at <http://www.kennedyslaw.com/article/3dprintedproducts/> accessed 20 December 2016.

[23] 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 <http://ec.europa.eu/DocsRoom/documents/17921/attachments/1/translations/> accessed 20 December 2016.

B. Product Liability

Available remedies for the users of defective products include the common law of contract and tort, and the UK Consumer Protection Act (CPA) 1987. The first hurdle to bringing a product liability claim would be to define what constitutes a 'product', and who the 'manufacturer' is in the production chain of bioprinted tissues and organs. Currently healthcare delivery is deemed as 'service' and the introduction of bioprinting process on-site may transform the nature of hospital healthcare provision from 'service provider' to 'products manufacturer'.[24] Hospitals, medical clinicians, and even software and CAD file designers, may then be expected to bear the liability of a 'manufacturer'.

Hospitals and healthcare clinicians are facing an undefined legal landscape of emerging 'medical products liability' by introducing RDM 3D bioprinting into their service. The legal definitions of 'product', 'defect of a product', and 'manufacturer' require further investigation. For a licensed product where a franchise-style arrangement is in place, the licensors will be expected to bear the liability. For unlicensed products, errors arising in the chain of custody will need identifying. Shared liability may be the way forward in cases where liability is impossible to separate from each other. It is less clear whether 3D scans and 3D bioprinting files are 'products' and that software and CAD file designers are deemed as 'manufacturers'. For products produced under the 'Specials' route, if the technician of a specials manufacturer discharged the tasks in accordance with a clinician's inappropriate specification, then it is the clinician's burden to prove whether he was acting with due diligence.

It is worth noting that the European Commission recently launched an evaluation of the Product Liability Directive. In particular, it attempts to examine the current product liability regime in relation to recent digital development. Considerations include: whether apps and non-embedded software are 'products' as defined in the Directive, whether an unintended, autonomous behaviour of a robot could be deemed 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.[25] The finding of the evaluation is expected to contribute to the further clarification of the ambiguities raised in this chapter.

[24] See the following discussion.

[25] 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/smart-regulation/roadmaps/docs/2016_grow_027_evaluation_defective_products_en.pdf> accessed 20 December 2016.

CHAPTER 5. INTELLECTUAL PROPERTY AND WATERMARKING

In this chapter we examine the feasibility of using an embedded watermarking system in the CAD file and in the printed objects, with a view to safeguarding the source, quality, and traceability of 3D bioprinting products.

The manufacture of a bioprinted implant using a 3D printer requires an accurate understanding of the physical and biochemical requirements for healthy cell growth and for integration. The main requirement is to ensure that good mass transfer occurs to permit an adequate rate of nutrition for the cells and timely elution of waste products from within the construct. The printing algorithm must deliver suitable internal scaffold architecture for cell attachment and growth and for mechanical integrity. There must be suitable management of edge effects, where the tracking of the printer head makes traverses to return across the work during the build. Without appropriate control software and specification that allows for the impact of these effects, the edges may be less porous than the bulk of the implant and may occlude mass transfer compromising construct health by restricting ingress of nutrients and egress of waste products. With this necrosis, perhaps accompanied by accelerated degradation of the scaffold structure where this is catalyzed by the lowered pH of such an environment, structural integrity may be compromised and the construct will fail to integrate into the patient's body. In practice this means that the findings of lengthy and expensive development phases of the innovation are going to be realised in the code and the constraints to the CAD for manufacturing the construct. There will be a lot of intangible value captured by the in-built controls and this must be protected in order to act as a barrier to entry of unfair competition.

The effects of using unsuitable software, for example, in a 'me-too' product that superficially resembles the legitimate one, may not be apparent for the first few days post-transplant, after which necrosis or structural failure may occur once the patient has returned home, and this opens the way for unscrupulous organizations to manufacture counterfeit products at a lower price using machines that are the same as those in properly-accredited facilities. However, such a situation is unlikely to provide sustainable business for criminals and it is more likely that a market in illegally-copied and illegally-distributed software, containing the correct coding, will grow unless steps are taken to prevent it.

Management of chain of custody

The distribution of the manufacture of medicinal products such as ATMPs carries with it the risk of introducing illicit raw materials and reagents, or counterfeit products into the chain of

custody. The inclusion of a three-dimensional 'watermark' in the construct is feasible provided that the local change in architecture does not compromise the product features listed above. Such a watermark would consist of a subtle but distinct variation in the width of struts and layers inside the construct in order to display an image in 3D that could be detected by tomographic scanning. However, such a watermark would not be apparent to the patient or their representative without the application of an MRI scanner or similar means of inspection; an impractical safeguard that could not be invoked until after the damage is done and one that would disappear over time in the case of constructs made using bioresorbable scaffolds.

More helpful is the use of bespoke culture and transfer units. A living construct relies upon maintenance of asepsis and nutrition during manufacture and transport to the operating room. Such maintenance can be provided by a closed cartridge within which a growth medium is contained and which is equipped with means of fluid management such as a recirculation loop with peristaltic pumping. The principles of such an aseptic cartridge can be seen in the tissue engineering system made by Octane, Inc. (the 'Cocoon')[26] and its precursor the ACTES system from Millenium Biologix, Inc.[27] Such a cartridge, supported by thermal control at 37°C and fluid management from a durable, returnable device, could be used as the basis of assurance of authenticity and quality if it is made to include recognition elements such as embedded readable microchips that can be verified at point of use. 'Smart ports' through which sterile medium is introduced could log the time of utilisation and, if verified by 21 CFR 11 compliant software and time-stamping,[28] could be used to upload a record of the management of the system throughout its trajectory to operating theatre.

Watermarking is the means we proposed by which to resolve many of the difficulties raised by RDM in 3DP in the biomedical sector. Watermarking can be utilized to track, trace and guarantee the quality of 3DP products. A watermark can act like a barcode, enabling professionals and end users to trace not just the product itself, but also the materials within the product and potentially the distribution lifeline of the product. Watermarks can be used to identify if a product is operating effectively and within advertised guidelines.

There have been many concerns about the quality of 3D biotech products, in particular the ability to ensure their quality in terms of source and in terms of continued operation. The use of watermarking is an efficient way to deal with those concerns. To date, there has only been

[26] Octane, '"See how" Octane Technology can impact your goals', <http://octaneco.com/octane-download.pdf> accessed 02 January 2017.
[27] U Meyer, J Handschel, HP Wiesmann, and T Meyer, 'Fundamentals of tissue engineering and regenerative medicine' (Springer Science and Business Media, Berlin, 2009) 607.
[28] FDA Code of Federal Regulations Title 21 Guidance for Industry Part 11 Electronic records; electronic signatures – scope and application [2003].

a limited attempt to barcode products used in the NHS.[29] Watermarking can contain much more information than a barcode, and it can also be edited. Furthermore, watermarks can be deeply embedded within products.

Watermarking also helps to confirm 3D printing as a viable means of providing healthcare. One of the issues to date with 3D printing is the ability to identify and confirm the origin of goods in a secure fashion, and to ensure that printed products meet the specifications required. Watermarking helps to do this because it can act as a secure system. Furthermore, the use of watermarking helps to provide a clear link to tortious liability, because it provides the evidentiary means by which to be able to establish who was responsible for actions such as the active printing, the act of manipulation, or an act of implantation. For instance, it would allow someone with a faulty implant to be able to establish whether it is faulty because of the implant itself, and it would help establish the origin of the goods.

3D printing has posed a number of challenges to intellectual property laws. Much has been written about the threat of piracy, in particular piracy involving 3D scanning of existing physical objects and where a 3D printer has the possibility of replicating that object.[30] Nonetheless, there is a highly significant issue that is beginning to arise that has received no attention, and that is the utilization of watermarking technologies within 3D printing, in particular bioprinting. Watermarking technologies have been protected under laws relating to copyright, but it is only recently that the technology has developed to such a extent that it can become a highly important component in the distribution of copyright works.[31] In relation to bioprinting, the use of watermarking goes beyond that in traditional copyright products. Whereas in traditional copyright products watermarking is mainly used for the purpose of tracking the use of products, with bioprinted products watermarks can be used to also guarantee the quality of the final printed product, as well as ensure the quality of the source materials. These are uses that were not envisaged by the legislation that is currently being used to protect them. This opens up the possibility of a lacuna of protection in certain specific circumstances.

[29] BBC, 'Breast implants and other medical items get safety barcodes' (BBC News, 29 December 2016) <http://www.bbc.co.uk/news/health-38403388> accessed 03 January 2017.

[30] C Anderson, Makers: The new Industrial Revolution (Random House Business Books: London, 2012); B Berg, S van der Hof and E Kosta, 3D printing: Legal, ethical and economic dimensions (Springer: The Hague, 2016); P Li, '3D Bioprinting technologies: Patents, innovation and access, [2014] 6 Law, Innovation and Technology 282; P Li, S Mellor, J Griffin, C Waelde, L Hao and R Everson, 'Intellectual property and 3D printing: A case study on 3D chocolate printing' [2014] 9, 4 JIPL&P 322; J Tran, 'To bioprint or not to bioprint' [2015] 17 North Carolina Journal of Law and Technology 123.

[31] J Griffin, 'A proposal for a doctrine of information justice' [2016] IPQ 44.

A. Legal regulation

Virtually all of the current regulation with regard to watermarking stems from the rules concerning copyright protection. These rules all derive from international agreements, as represented by the WIPO Performances and Phonograms Treaty 1996 and the WIPO Copyright Treaty 1996. Both have similar provisions. The WIPO Copyright Treaty Article 12 contains the most generic provision, which reads as follows:

> (1) Contracting Parties shall provide adequate and effective legal remedies against any person knowingly performing any of the following acts:
>
> (i) to remove or alter any electronic rights management information without authority;
>
> (ii) to distribute, import for distribution, broadcast or communicate to the public, without authority, works or copies of works knowing that electronic rights management information has been removed or altered without authority.
>
> (2) As used in this Article, "rights management information" means information which identifies the work, the author of the work, the owner of any right in the work, or information about the terms and conditions of use of the work, and any numbers or codes that represent such information, when any of these items of information is attached to a copy of a work or appears in connection with the communication of a work to the public.[32]

This in turn has been implemented through national legislation. This legislation is quite similar between the various signatory countries, but there are some significant differences. These differences tend to occur not from the specific provisions themselves, but from regional

[32] WPPT 1996 equivalent is Article 19: '(1) Contracting Parties shall provide adequate and effective legal remedies against any person knowingly performing any of the following acts knowing, or with respect to civil remedies having reasonable grounds to know, that it will induce, enable, facilitate or conceal an infringement of any right covered by this Treaty:
(i) to remove or alter any electronic rights management information without authority;
(ii) to distribute, import for distribution, broadcast, communicate or make available to the public, without authority, performances, copies of fixed performances or phonograms knowing that electronic rights management information has been removed or altered without authority.
(2) As used in this Article, "rights management information" means information which identifies the performer, the performance of the performer, the producer of the phonogram, the phonogram, the owner of any right in the performance or phonogram, or information about the terms and conditions of use of the performance or phonogram, and any numbers or codes that represent such information, when any of these items of information is attached to a copy of a fixed performance or a phonogram or appears in connection with the communication or making available of a fixed performance or a phonogram to the public'.

differences relating to the scope of copyright protection. Consequently, it is arguable that some types of watermarking may not gain protection in the United States, but may gain protection within the European Union or within the domestic UK provisions. These differences will be considered shortly, but for the moment it is necessary to turn to the national provisions in order to see their general scope.

The most developed provision is found in the United States within §1202 of the Digital Millennium Copyright Act 1998. This does not contain exclusive list of what could be considered a watermark. Significantly it does not use the word 'watermark' but instead refers, in the same way as international law, to copyright management information. Section (c) of the provision provides definitions and examples of what might be covered.

A similar provision exists within the European Union in Article 7 of the European Union Copyright Directive (EUCD) 2001. There is an implementing provision of the above EUCD article in the UK law, s.296ZG (7) Copyright, Designs and Patent Act (CDPA) 1988, which is very similar. As noted earlier, there are some potential challenges in relation to the scope of these provisions and their relationship to copyright. First of all, these provisions are based within copyright laws. It is possible to make the initial observation that copyright management information and watermarking within the UK or the European Union has to be attached to, or involve, a copyright work.[33] This is less clear in the United States because an associated provision - §1201 Digital Millennium Copyright Act 1998, which deals with digital rights management mechanisms - has been held to cover elements of works where copyright infringement has not been established.[34]

Another legal aspect that is worth briefly considering is the overlap with the watermarking technologies and patent law. It immediately has to be noted that the patent protection in this area would be over a particular form of watermarking technology, i.e. as an invention. It would not cover protection of the use of a watermark in the way that might occur under the CMI provisions discussed above. However, it would be useful to use the provisions if a novel watermarking approach is developed. This might be the case with regard to bioprinting, for instance, where technologies are developed to guarantee the quality of the original product. However, the long-term viability of these patents has to be considered because it is possible that they would be deemed overbroad in the same way that other biotechnology patents have also been in the past. Another issue that needs to be borne in mind is that in the UK computer software cannot be patented "as such" under s.1(2) Patents Act 1977, as is the case under the

[33] As per the wording in Article 7 EUCD and s.296ZG as quoted in the body text.

[34] A good example of this is the case of MDY v. Blizzard Entertainment [2010-11] US Court of Appeals, 9th Circuit 629 F.3d 928. (US Court of Appeals, 9th Circuit, 2010/2011).

European Patent Convention.[35] This means that the watermarking technology has to operate with e.g., a 'technical contribution' in the same way as a physical invention in order for it to be patented, or involve 'any hardware'.[36]

B. Watermarking: the technologies

Watermarking technologies come in a number of forms. Katzenbeisser and Peticolas[37] identified that there are passive and active watermarks. For instance a passive watermark simply identifies content, whereas a more active watermark would be involved in the actual policing of how the content is used. Likewise, there have been distinctions made between standard watermarking technologies which identify information such as who the author is, and fingerprinting technologies that are used for the express purpose of tracking content.[38] The latter can include algorithms that help to identify each unique piece of content. It is also possible to say that there are complex watermarks and simple watermarks; simple watermarks being again the transposition of basic identifying information, whilst complex watermarks are those that include complex algorithms to how content has been reused in particular ways by end users.

Subject to the above discussion as to whether a copyright work is or is not required (and thus the applicability of the copyright rules relating to subsistence), CMI data associated with 3D bioprinting could, in addition to standard identification and trace techniques, include clinical implant (cell-scaffold 'construct') characteristics that are described in the specification at four hierarchical levels: 1. specification of the continuous phase of the object (bulk properties such as void volume, mean strut thickness and its polydispersity, any anisotropic features and their contribution to the mechanical properties); 2. overall dimensional specification, to include: permissible ranges (lower and upper) for the critical dimensions of the implant (so as to ensure that implant failure will not occur either as a result of mass transfer needing to take place over too large a distance to permit maintenance of cells and/or angiogenesis, or as a fracture due to too thin a construct to support loading), and relationship of construct dimensions to the shape that will be tailored to the patient; 3. features of the edges of the construct that differ from the bulk properties such as the local solid volume as a result of the printer head skirting

[35] European Patent Convention Article 52/3 Convention on the Grant of European Patents [1973] ILM 13/268; UNTS /199 [1974].

[36] For the UK technical contribution approach see Aerotel Ltd v Telco Holdings Ltd Macrossan's Patent Application [2007] RPC 7; the EPO "any hardware" approach see DUNS LICENSING ASSOCIATES/Estimating sales activity (T154/04) [2007] EPOR 38.

[37] S Katzenbeisser and FAP Peticolas, Information hiding techniques for steganography and digital watermarking (Artech Books: Boston/London, 1999).

[38] See MGM v Grokster [2007] 518 F.Supp.2d 1197 CD Cal.

the edge of the CAD volume, and deliberate placement of reinforced zones or inclusion of eyelets to enable fixation; 4. the range of things that the surgeons are, or are not, allowed to do in the process of surgery (e.g. how much material may be cut away). Whilst 1 and 3 are prescriptive, 2 and 4 are constraints, but all are more in the nature of an active complex watermark rather than a passive one.

C. Attacks to watermarking technologies

Whilst the variation of watermarking technologies is immense, they are subject to very similar attacks. These include: *Jitter attacks* – *"*changing low-order bits in pseudorandomly selected locations in the signal"; [39] *Stirmarks* – which involves resizing an image that has undergone minor geometric distortion; *Mosaic attacks* – breaking down images into smaller sections and then reassembling them without the watermark; *Echo hiding attacks* – a form of iterative attack; *Inversion attacks* – by including a second watermark; *Collusion* – by comparing two different watermarks to remove the original; *Attacks using watermark detectors; attacks on copy control mechanisms* – to replicate the original content in its entirety and disable reporting software.

D. Specific issues for medicine / medical devices / ATMPs

With regard to utilizing watermarking to identify the source materials used in 3D printing a biomedical product it must be noted that simple materials are difficult to watermark, in which case it might be best to utilize more traditional track and trace methods found within existing distribution chains. However, the more complex the materials are the easier it is to embed a watermark to help to identify the origin of the material. Considering that developments such as 4D printing rely upon complex materials, and considering the usefulness of these materials in biomedical devices, it is quite likely that more complex source materials will be used. Consequently, the difficulties in tracing original content material that is simple in nature may be reduced by virtue of the fact that many printed objects will likely be using complex original source materials.

With regard to the utilization of watermarking to guarantee the quality of the final printed product, watermarks can be printed in the final object. The final quality of the watermark can

[39] S Shaw, 'Overview of watermarks, fingerprints, and digital signatures' [1999] EducatiOn-Line JISC Technology Application Programme <http://www.leeds.ac.uk/educol/documents/00001244.htm#_Toc456162860> accessed 19 December 2016.

be used immediately after print, and it can also be used in subsequent months and years in order to assess whether a product is disassembling or breaking down. If a watermark is printed within an object such as DNA, then there is the possibility of this watermarking technology to be able to trace reasonably precisely the manner in which any degradation is occurring.

Watermarking could also be used to help identify standards for medical devices. For instance, in China various stages of approval require different types of invasive procedures. It is possible that we could use watermarking in order to be able to meet those standards by, for example, being able to trace the origin of a complex source material, or to trace the continued viability of bioprinted procedures.

As for home-printed medicines, watermarking can again be particularly useful. It will help guarantee that the printed medicines are of sufficient quality, and ensure that the medicine is capable of being inspected for its continued quality after use, or its viability if the medicine has been waiting to be used after a period of storage.

E. Utilising new forms of technology

Watermarking is intrinsically related to the development of some of the newer technologies being developed in the field of bioprinting. For instance, watermarking has been used in relation to DNA printing. Microsoft are using DNA stored data.[40] A researcher in Slovenia has utilized watermarking technologies in order to identify seeds that are protected by intellectual property.[41] There is the possibility of storing watermarks in DNA similar to watermarks in computer software; the current CRISPR-Cas9 methods in common use today are capable of inserting watermarks into DNA through the simple processes of cutting and removing DNA in particular patterns.[42]

F. Limitations to watermarking technologies

The advantages of watermarking, such as the ability to trace products and to guarantee quality, are reasonably self-evident but there are some limits to its use. Perhaps the most significant is the fact that a watermark does not by itself help to prevent piracy. Whilst a watermark may be highly complex and difficult to reproduce using the same process of watermark production,

[40] Microsoft, 'DNA storage' [2015] <www.microsoft.com/en-us/research/project/dna-storage/> accessed 19 December 2016.

[41] K Fister, I Fister, J Murovec and B. Bohanec, 'DNA labelling of varieties covered by patent protection: a new solution for managing intellectual property rights in the seed industry' [2016] Transgenic Research, 1.

[42] Anon, 'The Age of the Red Pen' [2015] 416 The Economist 8952, 19-22; J Doudna and P Mali, CRISPR-Cas: A laboratory manual (Cold Spring Harbor Laboratory Press, New York, 2016).

if a file can be reproduced in its entirety then there is absolutely nothing that a watermark can do to prevent a reproduction being made. Indeed, this is the rationale in part behind the association of Digital Rights Management with watermarking in the United States' DMCA 1998. This association is key because digital watermarking is protected by Digital Rights Management, whilst watermarking in turn helps to ensure the efficacy of Digital Rights Management (DRM) mechanisms by providing identification information on content. DRM has a long history in the use of copyright content, but the application of DRM to biotech products is nowhere near so pronounced. Indeed, the applications which we are seeking to put watermarking to in relation to biotech products does not lend them to a co-terminus application with watermarking. A DRM system is unlikely to prevent the replication of a watermarked titanium bone. However, encryption systems could be used in association with a watermark (even seemingly within it) to help reduce the incidents of copying. For example, online verification could be used to ensure each product is unique. Likewise, the practice of barcoding products with patients could reduce piracy, and so could require watermark information to be verified on a central database. Furthermore, the use of a block chain could be one means by which to verify the origin of a watermarked product.[43]

G. Interim conclusion

The legal regime for protection of watermarks in biomedical devices is not straightforward. It is clear that watermarking can be protected under CMI if copyrightable content is involved, but this seems to be an unnecessary requirement for biomedical devices where copyright might well be a peripheral concern. Nonetheless, it would appear that many types of watermark can be so protected, and this is significant for those watermarks that are more complex in character and more likely to be active, i.e. in not merely detecting infringements but also in tracking use and quality of medical devices. If anything, this research reveals a need to be able to protect such watermarks that are free of copyright simply because the watermarks themselves provide an important means by which to guarantee the quality and source of 3D bioprinted products.

[43] See inter alia D Brown, 'Cryptocurrency and criminality: the Bitcoin opportunity' [2016] 327 Police Journal, 331-332; Office of the National Coordinator for Health Information Technology, 'Blockchain for Healthcare Proposal' [2016] <https://oncprojectracking.healthit.gov/wiki/download/attachments/14582699/48-Leidos%20Blockchain%20Proposal_v3.pdf?version=1&modificationDate=1474479420000&api=v2> accessed 03 January 2017; H Kartik and SG Yatish, 'Roadmap for a Controlled Block Chain architecture' [2016] <https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2822667> accessed 03 January 2017.

CHAPTER 6. CONCLUDING REMARKS AND FUTURE WORK

This project has examined the extent to which re-distributed manufacturing (RDM) in 3D bioprinting disrupts existing laws and legal regulations. There are a range of different possible business models for 3D bioprinting, 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 elsewhere. These models each imply different regulatory and liability scenarios.

RDM in 3D bioprinting presents a range of unprecedented quality challenges from a manufacturing process perspective, as well as challenging existing product regulation regimes. Computer-Aided Manufacturing (CAM) in the production process further compounds the thorny issues of risk management in the 'chain of custody' and the 'quality of materials', due to the involvement of various personnel during the operation process such as CAD file designers and surgeons. CAM greatly facilitates 3DP-RDM, but corresponding challenges relating to data control, data management, data protection, and privacy issues, remain to be addressed. Currently relevant legal frameworks struggle to cope with the disruptions brought by 3DP-RDM, unclear 'product' or 'service' classification in healthcare provision, and the ambiguities in respective clinical practitioners' duties and liabilities, all of which may deter the medical sector from using this nascent invention.

In order to map the gaps and uncertainties of RDM in 3D bioprinting in the regulatory sphere, we have analysed the key issues in four relevant EU/UK legal instruments, comprising the regimes covering tissues and cells, medical devices, pharmaceuticals, and Advanced Therapy Medicinal Products (ATMPs). It is unclear whether bioprinted products, repeated using the same manufacturing equipment 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' (HE) and 'Specials' regulatory product routes might accommodate RDM in 3D bioprinting.

With regard to product liability arising from RDM in 3D bioprinting, remedies could be sought from the common law of contract and torts, and the UK Consumer Protection Act (CPA). The legal duties of CAD file designers, surgeons, and hospitals, are in need of further clarification in order to delineate their respective liability. It remains to be seen whether hospitals will become a 'manufacturer' if they start to incorporate a 3D bioprinting unit on-site and/or in vivo. Current distinction between 'medical products' and 'medical service' and the nature of hospitals as a service provider will need further investigation.

Our finding indicates that appropriate software management and data specifications would be the key to data integrity. We therefore propose to evaluate the feasibility and efficacy of an embedded watermarking system used in software and products in order to safeguard the source, quality, safety, traceability, and intellectual property issues associated with the technology.

Overall, 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 methods for protection of IP and prevention of data privacy; the complexity of product regulation and the important relevance of exemptions in current regimes; how RDM 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 the current EU regime.

Appendix I: Focus group at King's College London

Focus group for the EPSRC project on mass customization governance of Redistributed Manufacturing (RDM) in 3D printing

Friday 4 November 2016

Venue: Dickson Poon School of Law, Kings College London, Somerset House East Wing, Strand, Ante Room SW1.17

Project Title: *A feasibility study of mass customisation governance: regulation, liability, and intellectual property of re-distributed manufacturing in 3D printing.*

Schedule:

10.30-11.00	Arrival (tea and coffee)
11.00-11.05	Introduction
11.05-12.05	One hour short presentations: • Nick Medcalf (Loughborough University) - Recent trends: Tech review & business models • Douglas Robinson (Institute for Research and Innovation in Society (IFRIS) / LISIS, Paris) - Scenarios of bioprinting • Phoebe Li /Alex Faulkner (University of Sussex) - Project presentation of the issues – Regulation and liability of 3D bioprinting • James Griffin (University of Exeter) - video presentation on watermarking and CMI
12.05-13.00	Q&A
13.00-14.00	Lunch
14.00- 14.10	Nick Medcalf: Case study intro
14.10-16.10	Alex Faulkner / Phoebe Li: Open discussion following 6 themes
16.10-16.40	Wine reception

Focus Group Themes:

- What are the applicable business models for bioprinting? Who is the manufacturer?
- What is the boundary to be drawn for licensable system/technology in terms of commercialisation? Prosthetic, machine, service, process - components of the process

- What should be the basis of assurance of quality? (Is a new form of oversight similar to the QP needed for assurance of quality and avoidance of unresolvable disputes as to failure made and fault?)
- What are the gaps in medical regulation and intellectual property rights, if any?
- What is a 'product'? Should a bioprinter be a medical device? Should CAD design files be deemed as 'product'?
- Cyber security/Data protection (patients' data and storage) and traceability. What is the role of software engineers and CAD designers' in product liability? How do we use digital rights management systems to control the use of printers?

Participant List:

- Dr. Phoebe Li, University of Sussex
- Professor Alex Faulkner, University of Sussex
- Katy Joyce, University of Sussex
- Professor Nick Medcalf, Loughborough University
- Dr. Daniel Thomas, 3Dynamics System
- Dr. Martin Baumers, EPSRC Centre for Additive Manufacturing, University of Nottingham
- Ms. Zita Jessop, NHS Plastic Surgeon
- Professor Iain Whitaker, Chair in Plastic Surgery, Swansea University
- Dr. Andrew Gleadall, University of Nottingham
- Dr. Douglas Robinson, Institute for Research and Innovation in Society (IFRIS) / LSIS, Paris
- Ms. Lucinda Evans, Brighton and Sussex Medical School
- Dr. Sam Roscoe, University of Sussex
- Phil Brown, Association of British Healthcare Industries (ABHI)
- Mr. Tom Dobbs, NHS Plastic Surgeon
- Dr. Andrea Matwyshyn, Northeastern University
- Dr. Mark Wickham, Alacramed
- Tomruk Ustunkaya, University of Sussex
- Jim Baker, Engineer, Renishaw
- Dr. Giulia Detela, Catapult
- Dr. Julie Allickson (via Skype), Wake Forest Institute for Regenerative Medicine

Appendix II: 3D Bioprinting Tissue Systems for Facial Transplantation with the NHS: Morrison Hospital

Daniel Thomas, 3Dynamics System

The Welsh centre for Burns and Plastic Surgery in Morriston Hospital are developing 3D bioprinted tissues made from human cells for use in future transplantation procedures. Their aim is for patients who have lost all or part of their ear or nose through trauma or cancer to have reconstruction using new tissue which is grown from their own cells. 3D printing technology is increasingly used to manufacture prosthetics and implants from materials including plastic or titanium.

However, 3D bioprinting using human cells instead of man-made material is still a novel science. The team have already succeeded in bi-printing small pellets of living tissue, proving that delicate cells can survive the 3D bioprinting process.

They have also developed a jelly-like support structure that can be used as the ink for printing the intricate shape of an ear or nose and, critically, that is compatible with the human cells. The next stage is to blend the jelly and cartilage cells together and 3D-print them into bespoke tissue for reconstructive surgery. The resulting part will need to be strong enough to not only withstand the surgical procedure to attach it to the patient, but also survive indefinitely as healthy tissue afterwards.

This tissue engineering process in ongoing but it is anticipated that real-life surgical trials could begin in as little as 3-4 years' time. Professor Iain Whitaker, Consultant Plastic Surgeon and Chair in Plastic and Reconstructive Surgery at Swansea University Medical School, is heading up the team. He explained: "We want to try and help people who were born with defects, or who have lost parts of their ear or nose as a result of trauma or cancer. We are using human cells, growing them up, to combine them with a printable material, 3D print them and implant them into the human body."

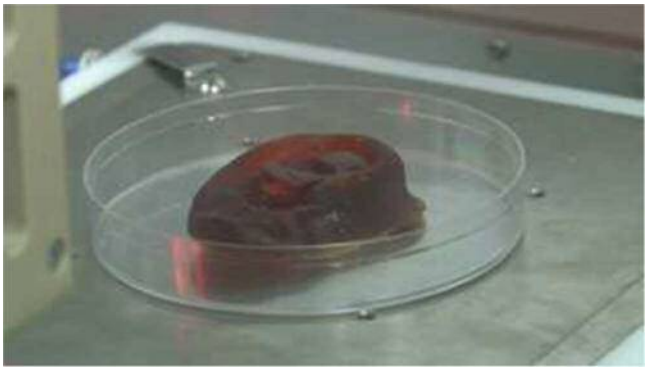

Image: High resolution ear structure bioprinted (this was a biologically inert structure).

This work is at the relatively early stages of development and requires combining many areas of expertise including biology, engineering and surgery. Current work includes growing a large numbers of cells in order to print larger constructs. A number of tests are required in order to ensure that these constructs will be stable enough to be used to implant into a patient. Professor Whitaker says “I would say that in two-three years we should be in a position to trial with animals, and within a year after that - pending ethical approval - we should be in a position to trial this in humans.”

This research is being focused not towards fueling the excitement of organogenesis, but instead towards producing heterogeneous biological support tissues for use in reconstructive surgery.

Image: A tracheal pre-tissue produced using 3D Bioprinting and the resulting Chondrocyte-based tissue after two days of maturation.

This research concentrates on using the natural self-organising properties of cells in order to produce a functional tissue that has measurable mechanical, metabolic and functional

properties. Through utilising stem-cell differentiation this can lead to the fabrication of vascularised and innervated tissues. This 3D-bioprinting technique works by depositing a biologically active gel containing two million chondrocyte cells per millilitre, together with alginate, hyaluronic acid, transforming growth factor β1, antibiotics and gelatine.

It is hoped that in the long-term this research will develop bioprinting as a process that can be used to produce multiple tissue types for use in operative repair materials or in the short-term for pharmaceutical trials. This next step in the development of this process could one day transform the field of reconstructive medicine which may lead to direct bio-engineering replacement human tissues on-demand for transplantation.

Appendix III: List of legislations

Berne Convention 1886.

Cartagena Protocol on Biosafety to the Convention on Biological Diversity 2003.

Commission Directive of 13 June 1991 laying down principles and guidelines of good manufacturing practice for medicinal products for human use [1991] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31991L0356&rid=1> accessed 22 September 2016.

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [2004a] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0094&rid=2> accessed 21 September 2016.

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0028&rid=3> accessed 20 December 2016.

Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells [2006a] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016SC0127&rid=1> accessed 20 December 2016.

Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirement, notification of serious adverse reactions and events and certain technical

requirements for the coding, processing, preservation, storage and distribution of human tissues and cells [2006b] <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006L0086&rid=1> accessed 20 December 2016.

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