RiHN
Redistributed Manufacturing in Healthcare Network

Redistributed Manufacturing in Healthcare

Creating New Value through Disruptive Innovation

WHITE PAPER

Wendy Phillips, Nicholas Medcalf, Kenny Dalgarno, Harris Makatsoris, Sarah Sharples, Jag Srai, Paul Hourd and Dharm Kapletia

Preface

Redistributed Manufacturing (RDM) in healthcare has the potential to transform the way in which medicines are supplied within the healthcare sector. It has the potential to make the system much more resilient and responsive and may lead to significant simplification of the supply chain. In addition, the use of additive manufacturing systems can completely transform how medicines are delivered to patients in terms of both new combinations and entirely new formats. The advantages of manufacturing medicines specific to a single patient include offering a previously impossible level of personalisation. Doses and courses of treatment are no longer limited to standard pack sizes, allowing therapies to be specifically tailored. The ability to combine drugs in a single tablet will improve compliance and the potential to control release characteristics offers a new level of complexity.

The ability of these advances to transform the delivery of medicines coincides with the NHS recognising the need to embrace the advantages of personalised medicine. In this respect RDM represents a critical enabling technology that will be essential if the full benefits of personalised approaches are to be realised. Clearly the adoption of this technology creates many issues that need to be addressed. The way in which medicines are regulated will need to be fundamentally rethought and the role of pharmacists in overseeing the process of dispensing will be transformed. These are not trivial issues and the safety of patients must remain paramount in the introduction of this new technology.

The time to plan for this transformative change is now. The technology is rapidly developing to offer new and hitherto unthought-of ways of delivering medicines. The challenge will be for all those concerned with the supply of medicines to recognise that this change is coming and the urgent need to plan for and take advantage of the opportunities it offers.

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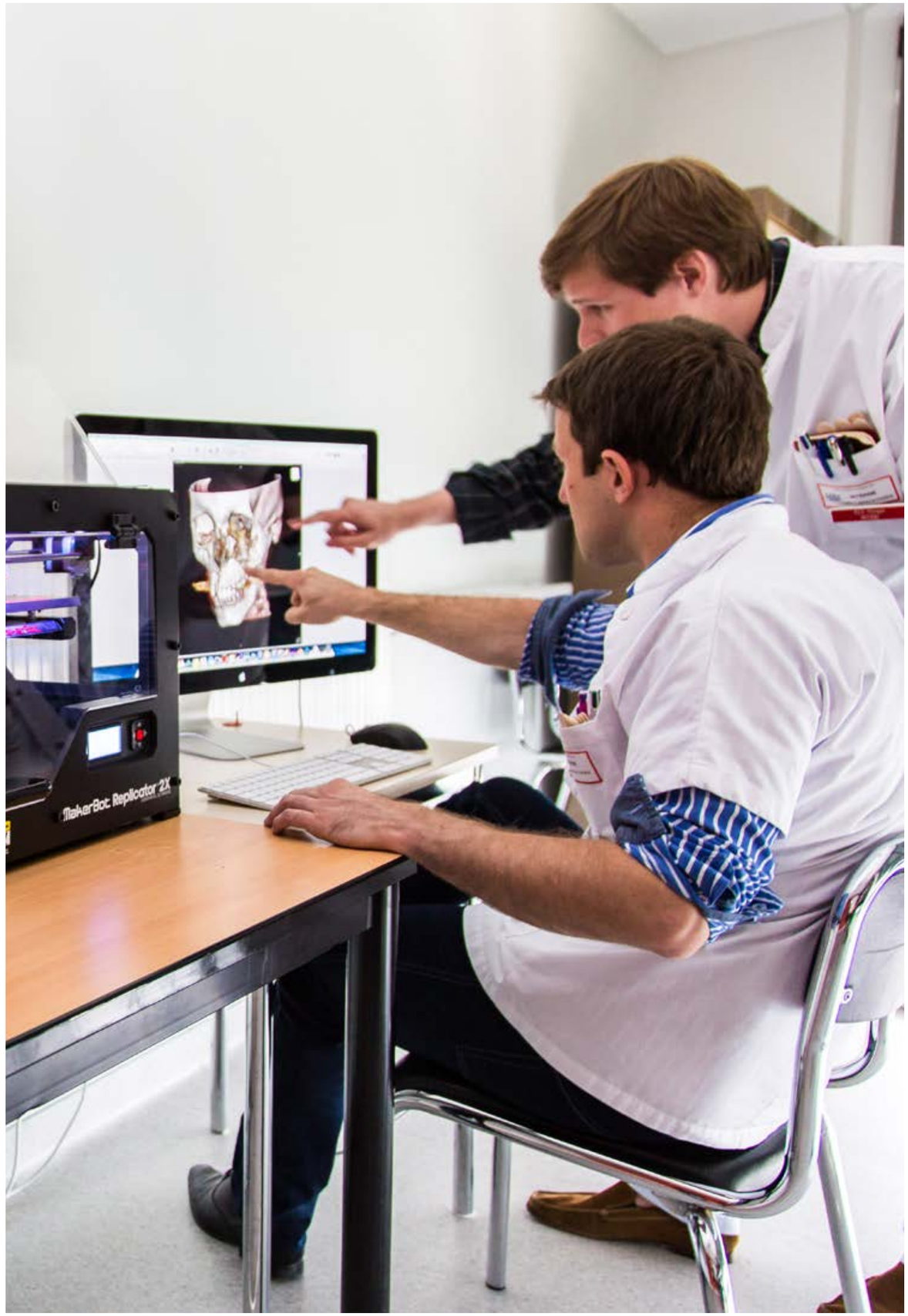

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Foreword

Welcome to the Redistributed Manufacturing in Healthcare Network (RiHN) White Paper. This is one of the core outputs of the RiHN, funded by the Engineering and Physical Sciences Research Council (EPSRC). RiHN brings together a multi-disciplinary network of academics, stakeholder organisations, clinical groups and industry to provide a forum to define the challenges of realising Redistributed Manufacturing (RDM) in healthcare. RiHN provides academic leadership, advancing real world applications of RDM in healthcare through engagement with relevant academic and user communities by conducting exploratory sandpit events, user engagement meetings, and supporting five feasibility studies exploring the potential for RDM in healthcare.

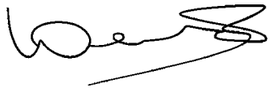
We take RDM to mean "Technology, systems and strategies that change the economics and organisation of manufacturing, particularly with regard to location and scale" (EPSRC, 2014). This recognises that the first stage of manufacturing evolution was the network of localised workshops in small towns and villages. The second stage was the creation of centralised factories to realise economies of scale. We now live in an age where several motives exist for redistributing manufacture, including cost reduction through terminal customisation; just-in-time delivery, particularly of perishable healthcare goods; management of capacity by distributing production through scale-out, rather than scale-up; and reducing up-front capital cost by building small production units in an incremental response to increase in demand.

There are important research challenges to realising these benefits in healthcare industries: technical needs must be satisfied to the appropriate regulatory standard; new patterns of training and retraining must be established to maintain operating quality from a distance; social and interpersonal features of these new ways of working must be addressed in ways that enhance quality of life and build quality assurance into the business structures; and new relationships must be forged between suppliers, service providers and users.

The RiHN White Paper is the first dedicated report on the RDM landscape in healthcare, covering early-stage needs, challenges, and priorities. The UK has the opportunity to lead in this area, and we have identified an extensive number of areas for fruitful R&D, crossing production technology, infrastructure, business and organisations. The paper serves as a foundation for discussing future technological roadmaps and engaging the wider community and stakeholders, as well as policy makers, in assessing the potential impact of RDM. Our findings are of particular value for policy implementers and funders seeking to specify action and to direct attention where it is needed.

The paper is also useful for the research community, to support their proposals with credible research propositions and to show where collaborations with industry and the public sector will deliver the most benefit.

Post-Brexit, there are a number of high-profile policy drivers increasing the attractiveness of RDM. These include the notion of reshoring manufacturing capability, further developing domestic high value manufacturing and associated skill-sets, exploiting opportunities for more sustainable and resilient manufacturing operations and supply chains, and defining a regulatory framework and standards that will make the UK a world leader in RDM.



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Executive Summary

Healthcare systems across the globe are under pressure to deliver affordable healthcare whilst addressing the needs of an aging population, and the demand for specialist and novel treatments. Events such as pandemics and terrorist attacks add more stress to a stretched system, impacting quality of patient care and healthcare budgets. There is an urgent need for cost-effective technologies that can provide right-first-time treatments, on demand, close to the point of need, reducing the number of repeat visits to healthcare professionals and avoidable take-up of hospital beds, thus alleviating pressure on the healthcare system.

> "[Re]distributed manufacturing will disrupt traditional labour markets and the economics of traditional manufacturing."
>
> **WORLD ECONOMIC FORUM (2017)**

The convergence of new service demands with new manufacturing technologies presents opportunities to address these challenges, particularly as we are heading towards an era of therapies that are tailored to individual needs and physiological characteristics. The potential of innovative technologies and systems that bring manufacturing closer to clinical need by means of redistributing manufacturing represents a transformative departure from the current system.

The UK has a strong network of proactive research-oriented universities, particularly in the fields of medical research and manufacturing engineering. However, it has not been clear what research is required to realise the potential of innovative manufacturing technologies and systems that enable local production of medical products and therapies. The RiHN White Paper represents the first serious attempt to gather expertise and to explore applications in promising areas of healthcare that could benefit from redistributed manufacturing.

Key priorities for future research and development include focusing on:

1 The development and performance of manufacturing technologies (including hardware, mechanisation, software, and programmable components)

2 Developing industry consensus on need and expectations for the development of technical standards for manufacturing technologies and critical components

3 An innovation-centred, systems-based model for human capital development to support advanced manufacturing technology innovation

4 Quantitative, real-time analytical technologies and corresponding data analysis tools

5 The discovery and identification of quantifiable measures of product quality

6 Advanced data analytics, machine interconnectivity and real-time acquisition, management and security of multiple sources of data

7 The potential impact of automated production platform technologies on product market approval pathways

8 The impact of emerging healthcare sector specific RDM strategies on extant legal and regulatory governance frameworks

9 Extending the UK's ability to provide the relevant specialised regulatory science skills for emerging manufacturing technologies and advanced therapies

10 Compiling the clinical and economic evidence base

11 Raising the level of organisational capability readiness

12 Formulating alternative financial reimbursement models

1 Redistributed Manufacturing in Healthcare

> "The factory of the future may be at the bedside, in the home, in the field, in the office and on the battlefield."
> **(FORESIGHT 2013: 20)**

The UK Government's 2013 Foresight Report on the future of manufacturing predicted major transformations in the nature of production that will challenge the healthcare industry. Emerging technologies will enable healthcare manufacturers to deliver products more rapidly, at a lower cost and in a more sustainable manner – "the factories of the future will be more varied, and more distributed than those of today" (Foresight, 2013).

How can this be achieved? The RiHN White Paper presents a paradigm shift in manufacturing termed "Redistributed Manufacturing" (RDM), that has the potential to address current healthcare system challenges. The redistribution of manufacturing in healthcare will involve physically shifting manufacturing systems closer to the point of clinical need, offering healthcare stakeholders increased control over quality, quantity and cost. RDM favours smaller-scale localised manufacturing units, typically enabled by innovative manufacturing technologies such as additive manufacturing and advanced robotics, complemented by advances in diagnostics.

A recent UK government report (Freeman, 2015) states that around 222,000 people are employed by 5,633 firms across the medical technology and biopharmaceutical sectors, generating over £60bn per annum. The greatest employment growth is in emerging sectors such as digital health, which have seen annual growth of 23 per cent between 2010 and 2015. Technological advances are bringing us closer to realising a more personalised form of healthcare, with exciting developments in genomics, diagnostics, and customised product designs. The ability to *manufacture* devices, advanced therapies and medicines at the point of care and need is a critical part of this emerging picture, underpinned by leading edge developments in precision manufacturing (KTN, 2013). RDM is a key enabler for the delivery of personalised healthcare, potentially accelerating access to treatments and superior products. The UK's strong science, engineering and commercial base is well positioned to compete in this arena.

Photo US Department of Defense

> “The creation of a new, more dynamic, flexible redistributed manufacturing sector may help to retain high-skilled graduates in this area. But it is likely that this new sector will require graduates with skills in STEM as well as business management and organisation: educational facilities may need to adapt their programmes to provide such skills.”
>
> **CAMBRIDGE INSTITUTE FOR SUSTAINABILITY LEADERSHIP (2017)**

RDM presents a radical way forward for incumbent manufacturers to branch into a new area, as well as opportunities for new entrants and partners to disrupt existing systems. However, much of the existing manufacturing infrastructure, quality systems, regulatory and governance frameworks, business models and organisations are tied to traditional modes of operation, typified by centralised off-shore mass production and large-scale economics. Many past national initiatives in manufacturing innovation have focused on engineering breakthroughs, such as increased automation and robotics on assembly lines, and optimising production processes. Whilst this may help maintain the competitiveness of existing business models, it is sub-optimal for the upcoming revolution in personalised healthcare.

“Distributed manufacturing is expected to enable a more efficient use of resources, with less wasted capacity in centralised factories. It also lowers the barriers to market entry by reducing the amount of capital required to build the first prototypes and products. Importantly, it should reduce the overall environmental impact of manufacturing” (World Economic Forum, 2015). Whilst there are compelling reasons driving RDM, the move from a centralised towards a decentralised model

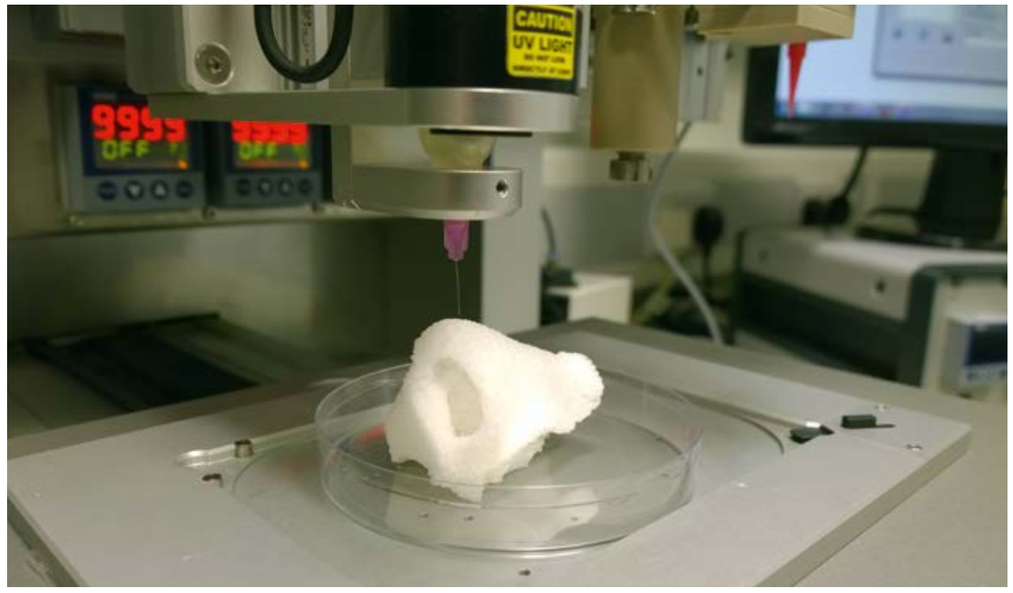


Photo University of Nottingham

will significantly impact manufacturing practices, particularly as the lines become blurred between physical production and point-of-care service delivery. For example, regulatory compliance and quality assurance will need to be adapted for multiple locations, making it necessary to ensure site-to-site comparability of manufacturing, as well as clinical processes and handling.

Whilst a compelling driver such as reducing costs often takes precedence in manufacturing and service organisations alike, a total systems perspective is needed for RDM, taking full consideration of investment versus return, patient benefit, and systemic dependencies that typify change and transformation in complex healthcare provision. The RiHN programme has examined *system readiness* for RDM in healthcare and identified a range of research challenges that must be addressed to make the UK a world-leading and serious contender in this arena. Much of this effort requires a targeted approach of investing in early-stage technology and manufacturing research, which is outlined in this White Paper.

1.1 The Redistributed Manufacturing in Healthcare Network (RiHN)

RiHN brought together a multi-disciplinary team of academics and practitioners and delivered a variety of workshops covering new areas of investigation, technology roadmapping, supply reconfiguration and regulation (see figure 1).

RiHN funded five feasibility studies covering potential applications of RDM in areas involving cell microfactories and various forms of 3D printing (advanced therapies, diagnostic medical devices and single dosage pharmaceuticals).

The programme benefited from close engagement with the healthcare industry with specialists from manufacturing and engineering, management, law, consulting, medical devices, regenerative medicine, health services, and pharmaceuticals (see Appendix C for more details). The strength of this White Paper is that it combines key stakeholder expertise from a range of diverse backgrounds, enabling a multi-disciplinary perspective on the future of RDM in healthcare.

The team was supported by an active advisory steering group, with representatives from **Innovate UK**, **Lime Associates Ltd**, the **Knowledge Transfer Network (KTN)**, and the **West of England Academic Health Science Network (WEAHSN)**. The advisory group provided expert steering, access to key stakeholders, and contributed to the independent assessment of feasibility study proposals.

Innovate UK
Knowledge Transfer Network

Lime Associates
The HealthTech Business Consultancy

West of England Academic Health Science Network

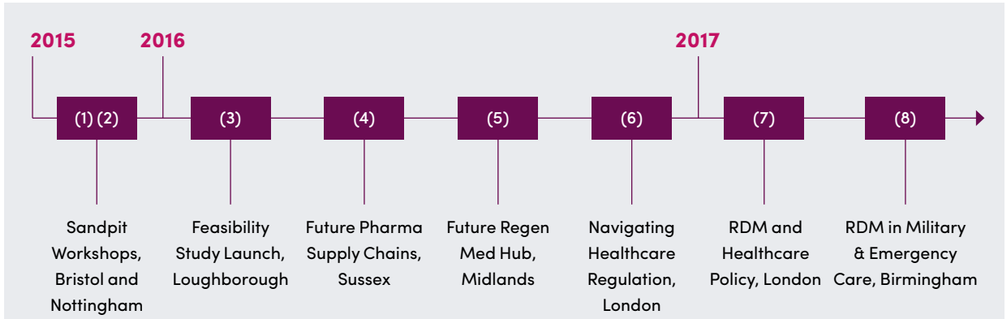


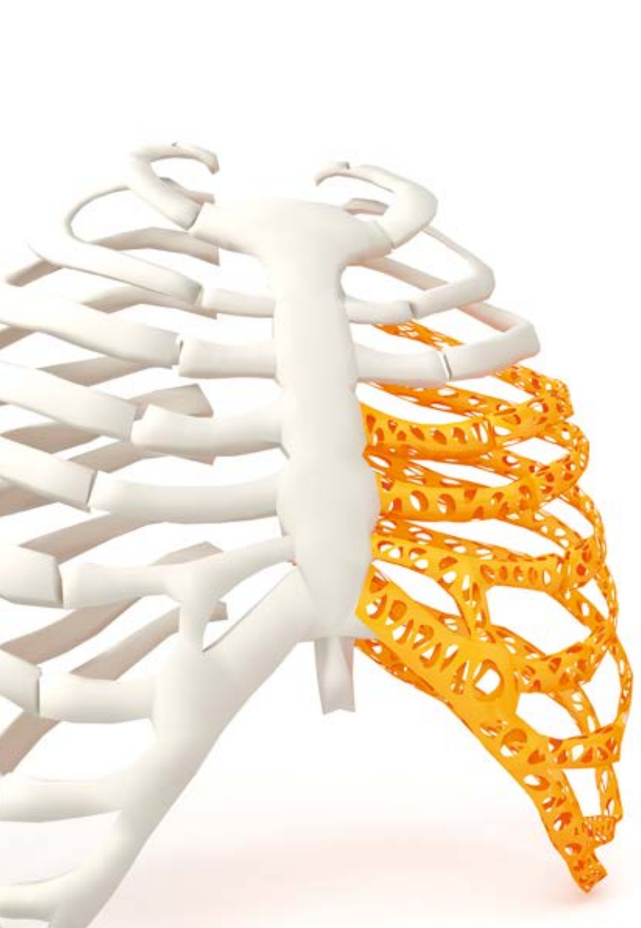
Figure 1 Timeline of RiHN events

RiHN developed a membership database of 232 individuals who have helped us advance the agenda of RDM in healthcare. Around 40% of these members are from outside academia, with 44 from government and the public sector, 31 from SMEs, 12 from Large Enterprises, and four from other types.

1.2 Emerging trends

Although RDM has the potential to deliver cost-effective treatments close to the point of need, many challenges remain and intensive research is required in the following critical areas:

Medical Devices and Diagnostics – RDM could have a significant impact in areas such as the manufacture of orthoses and prostheses (load-bearing medical devices), providing improved products with fit and function customised to the anatomy of the patient. Through RDM, devices could be manufactured within a single visit to the clinic, reducing wastage, trauma to patients and associated resource costs. This is of particular value when fitting orthoses and prostheses for children, whose rapid growth often demands frequent revisions and alterations. The manufacture of specialist diagnostics enabling real-time analysis is also a highly desirable outcome, particularly in cases where patients can monitor their own health.



Pharmaceuticals – Future configurations of supply chains for drugs and medicines suggest RDM could drive down the large-scale waste and inefficiencies associated with current business operations. Scenario analyses considered pharmaceutical manufacturing models, such as:

(i) 'Factory-in-a-box' – small-scale localised manufacture using continuous processing models, that require milder processing conditions and are more capital/energy efficient, that could be replicated in mobile 'container' units supplying local and/or niche volume requirements.

(ii) 'Print-on-demand' tableting at selected pharmacy outlets for medicines requiring multiple dose formats.

(iii) 'Make-at-point-of-use', in the home or in a hospital, for selected liquid or semi-solid drugs.

(iv) 'Medicines supply and replenishment' linking directly to patient management 'App data' on usage, and/or diagnostic device data on drug efficacy and/or patient medical condition.

RDM may help bring about a 'closed loop treatment' system, covering diagnosing patient dosage requirements, which would be enabled by made-to-order treatments and remote monitoring. The current system relies on electronic health records and has to deal with issues such as low patient compliance.

> "We're now living in a society where customers and consumers increasingly expect a high degree of personalisation, with bespoke products delivered next day which meet their needs exactly."
>
> **ADDITIVE MANUFACTURING STRATEGY (2017)**

"Distributed manufacturing will become the norm, with producers augmenting their traditional production footprints with smaller and more flexible units located next to points of consumption, allowing them to meet local requirements with a more responsive supply chain."

WORLD ECONOMIC FORUM (2017)

Regenerative Medicine – the highly specialist nature of advanced therapeutic products lends itself to RDM. Cell and tissue-based therapies (CATBTs) represent a cutting-edge and commercially interesting area of medicine for treating complex conditions, using living cells to restore human body function and resolve disease. CATBTs have expensive and time-sensitive supply chains. Drivers for RDM are primarily related to cost, capital and capacity. These include factors such as irrecoverable sunk costs in large centralised facilities, managing complex supply chains, and low temperature transport to ensure cell preservation. Responsive manufacture coordinated with clinical use is preferred, especially if cryopreservation is required.

Healthcare Infrastructure is a critical factor in the future development of RDM and raises issues around the management of chain of custody; assurance of quality; resolving the matter of when 'manufacturing' becomes 'practise of medicine'; suitable models of operation with risk-sharing and appropriate indemnification by differing organisations; and management of training standards for operators who are working far from the central manufacturer. Consideration of roles, skills and communications are key to ensuring that changes to infrastructure are considered holistically and from a systems perspective.

In summary, looking across emerging applications of RDM in healthcare, there is considerable scope to understand the evidence base for potential value propositions, allowing for a more informed comparison of benefits between centralised and redistributed models of manufacture. An in-depth analysis of data is required related to shelf-life and sensitivity of goods, logistical costs, patient outcomes between standardised and personalised treatments, and total production costs over time.

Taking RDM into static clinical settings near the patient still assumes geographically defined operating environments as well as the ability to support the treatment of chronic conditions. An interesting future possibility would be to take RDM into mobile or flexible locations, in cases where there is an acute and urgent demand for medical products or supplies, for example to meet the demands of humanitarian crises, natural disasters or emergencies. The first hours are critical for saving lives or reducing the chances of debilitating conditions; RDM systems could seek to deliver rapid diagnosis, production and testing in remote conditions.

1.3 Example research projects exploring the application of RDM

RiHN funded five feasibility studies exploring applications of RDM in healthcare, such as cell micro-factories, 3D bioprinting, pharmaceutical supply chains, and production of medical devices by the consumer (prosumer).

Cell Micro-factories and the Manufacture of Cell and Tissue-Based Therapies (CATBTs)

Led by the Centre for Biological Engineering, Loughborough University

CATBTs presents a cutting-edge area of medicine for treating complex conditions using living cells to restore human body function and resolve disease. CATBTS have expensive and time-sensitive supply chains; responsive manufacture coordinated with clinical use is preferred, especially if cryopreservation is required. Recent attention has focused on cell micro-factories – automated manufacturing platforms that enable CATBTs to be made at a higher degree of reproducibility than via manual operation.

The team found that RDM provides opportunities for a range of final manufacturing points, from regional hubs to small units next to the patient's bedside. Significant developments in online monitoring and culture automation are required – automated platforms need to digitally monitor and manage patient and product requirements, but be flexible and replicable. Quality control systems must be non-destructive, providing close to real-time measurement.

Progressive introduction of small manufacturing units to a common design, increasing the number of units in response to growing market size, is attractive in an economically challenged investment environment, overcoming the barrier of raising capital and reducing the risk incurred when committing all capital costs up-front.

Research Team

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3D Bioprinting of Islet Micro-tissues to Redistribute Manufacture for Treatment of Type 1 Diabetes

Led by School of Mechanical & Systems Engineering, Newcastle University

Diabetes is a global problem contributing to escalating healthcare costs worldwide. Ten per cent of the NHS annual budget is dedicated to treatment of diabetes and its complications. Type 1 diabetes is typically treated by careful monitoring of blood glucose levels and insulin replacement therapy. In some cases where glucose is particularly unstable, insulin replacement therapy is not enough and transplant options must be considered. Islet transplantation is a non-invasive 'micro-tissue'-based cell therapy presently aimed at restoring function by isolating islets of Langerhans from a donor pancreas and infusing these islets into the portal vein where they engraft and produce insulin. Presently, many islets are lost prior to engraftment. One of the major driving forces for these losses is the highly variable nature of isolated islets.

The main focus of the feasibility study was to develop a method for 3D bioprinting of islet-like micro-tissues with the aim of redistributing the manufacture of advanced ß-cell replacement therapies for the treatment of Type 1 Diabetes (T1D). The proposed redistributed manufacturing supply chain of ß-cell replacement therapy for treatment of T1D has been centred on a cost-effective treatment delivery with less patient reincidence and expanded access to this cell therapy.

Considering all of the different stakeholders involved in the islets' product supply and transplant chain, the proposed modifications will provide a more uniform product of greater consistency at transplant centres, improving clinician confidence as well as patient outcomes. In the short run, this will save the NHS money by reducing the number of procedures required to achieve this cost-beneficial treatment. In the long run, the outcomes of this project may open this treatment to a wider patient pool providing cost-beneficial treatment to a much wider demographic.

The emergence of 3D bioprinting provides a novel approach to islet transplantation and has the potential to improve viability of islets. This tool provides a platform to not only improve on existing transplant outcomes but to do so in a way that satisfies the regulatory need for better defined, more homogeneous cell therapies, eliminating lot-to-lot and intra-product variability. This provides the critical opportunity to define an ideal product specification for islet micro-tissue products.

Research Team

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Redistributed Manufacturing for Home-use Medical Devices

Led by Regional Medical Physics, Newcastle upon Tyne Hospitals

This feasibility study assessed the scope for localised, close-to-patient manufacture of home-use medical devices, using a single-patient-use urine flowmeter to develop proof of concept. Various additive manufacturing technologies were considered and fused deposition modelling (FDM), one technique used for 3D printing, was found to be superior in terms of safety, accessibility of equipment, cost and usability.

Through RDM, the production process for medical devices has the potential to become leaner, more agile and flexible, enabling a 'make-to-order' rather than a 'make-to-stock' approach. Having mapped the supply chain for the flowmeter case, it was found that shifting production close to, or at the point of need/use, could lead to time, cost and sustainability benefits. RDM could also lead to social benefits: local, at-home production reducing the need for hospital visits, minimising stress to the patient and the healthcare system. However, more work is required to overcome technical challenges around metrology and human factors related to adoption.

Specialist distributed providers (e.g. pharmacies) could be first adopters of a RDM model, although they would assume the regulatory responsibility of a manufacturer. Critical success factors will depend on the effective configuration of operational responsibilities shared between manufacturer innovators, infrastructure owners and end-user operators. Ultimately, RDM could progress to a point where some devices could be manufactured in the home by the patient (or prosumer) but production engineers must think differently and design for simplicity, ease-of-use, and work with materials that favour local production.

Research Team

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Enhancing the Resilience of Pharmaceutical Supply Networks: the Role of Redistributed Manufacturing

Led by School of Business, Management and Economics, University of Sussex

Posing the questions: "How can the adoption of redistributed manufacturing systems enhance the resilience of supply networks?" and "Where can redistributed manufacturing add the most value in pharmaceutical supply networks?" the University of Sussex investigated the adoption of RDM systems in pharmaceutical supply networks.

Undertaking an empirical study with participation from leading industry experts and academics in the fields of innovation, 3D printing/additive manufacturing, life sciences and pharmaceuticals, the University of Sussex found that pharmaceutical manufacturing incumbents are resistant to RDM or do not yet recognise the benefits of this approach. Because incumbents have sunk capital costs in existing infrastructure and long-established ways of working, RDM poses challenging questions for them.

The researchers suggest RDM should not be presented as a replacement, but as a complementary model that can run in parallel with existing operations, enabling organisations to position themselves close to points of need, affording greater flexibility, responsiveness and resilience. The Sussex researchers advocate further proof of concept activities to demonstrate the benefits of RDM to the pharmaceutical sector. Although RDM is currently regarded as a niche activity, research participants from the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) and Medicines Manufacturing Industry Partnership (MMIP) are exploring the potential of RDM to enable localised production of small molecules. As discovered by this feasibility study and other researchers, a critical factor regarding commercial adoption will be the reduction of production timescales to meet demand.

Research Team

C. Blome, S. Roscoe

School of Business, Management and Economics, University of Sussex

3D Bioprinting: Commercialising Personalised ATMP/ Device Combination Products

Faculty of Engineering, The University of Nottingham

Recent developments in bioprinting capabilities have made it possible to manufacture customised implants tailored to a specific patient. Patient data is used to generate 3D models that tailor treatments to individual patients. The relatively low cost and simplicity of bioprinters make them an ideal candidate for RDM. Currently Advanced Therapy Medicinal Products (ATMPs) are not bio-printed by any businesses. The team at the University of Nottingham set out to establish the barriers to commercialisation by drawing on empirical data collected through engagement with a variety of experts including clinicians, equipment suppliers and tissue engineering researchers.

The study shed light on the changing roles deriving from the novel supply chain, e.g. when hospitals become factories, and on how the NHS and commercial activities might integrate. The research signposted future trends in the regulations, raising awareness of opportunities and challenges for enterprise in terms of emerging business and governance models. For example, existing regulatory frameworks have not yet addressed the differences between products manufactured by bioprinting technology and those manufactured by conventional, more craft-based methods. With close lines of communication with the UK regulator, the study contributed to understanding the likely pathways that 3D bioprinting can take in the UK and EU.

Research Team

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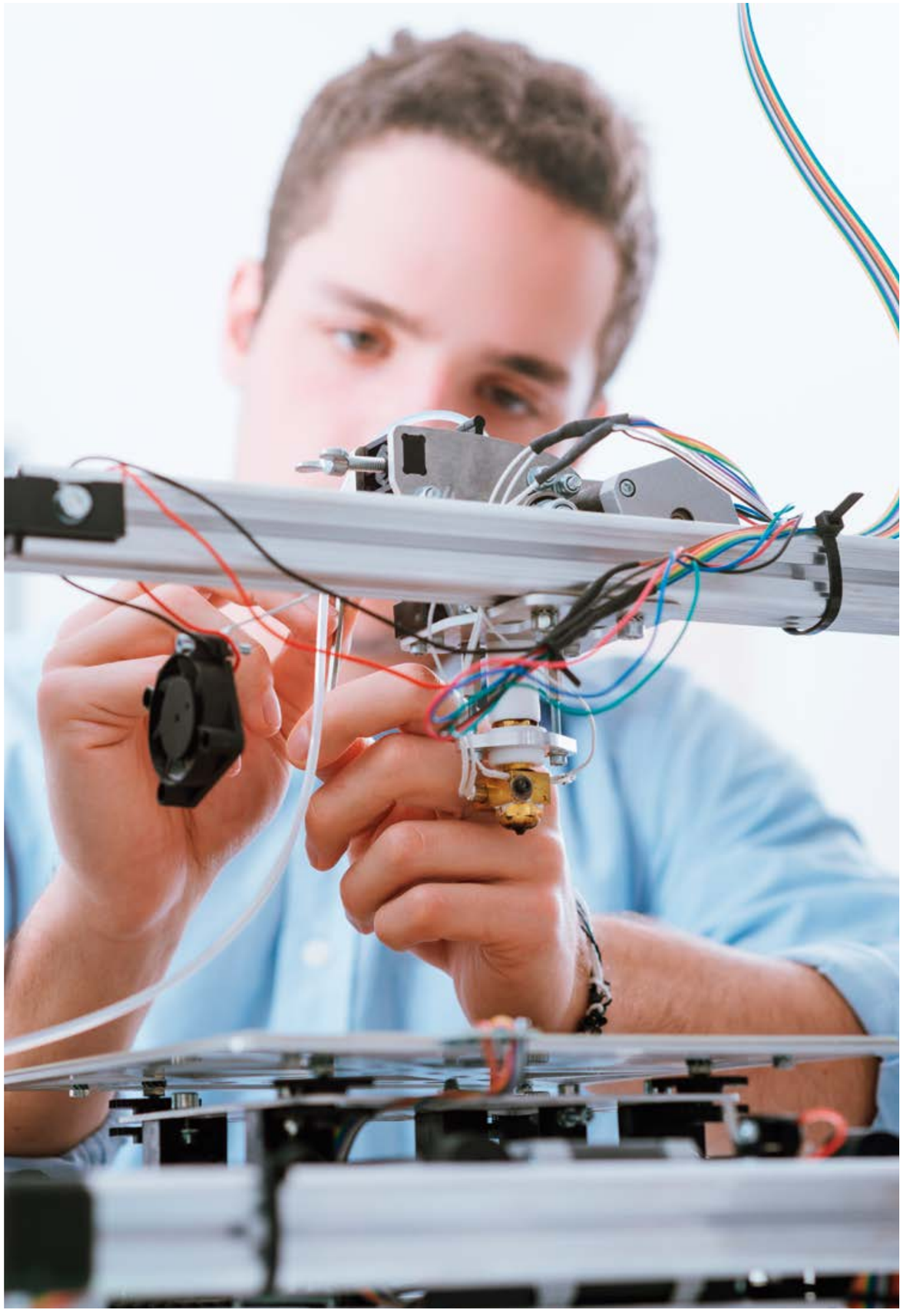
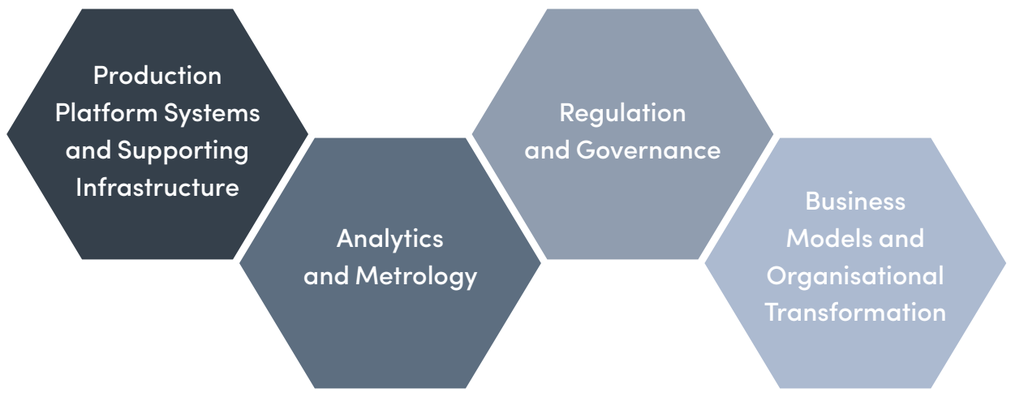


2 Needs and Challenges

A comprehensive review of the research material generated by RiHN identified future capability needs as well as generalisable translational and transformational challenges that must be overcome if the potential of RDM applications is to be realised.

In the healthcare context, RDM will be adopted by the development of innovative automated multi-product, multi-material, additive layer or CATBT production platforms that can be located in multiple sites at or near the point of care, which is intrinsically dependent on the product type and the degree of personalisation. Adopting a systems view, RiHN has identified four key interrelated challenge themes that distinguish RDM from the current centralised production paradigm.

The first two thematic areas describe the challenges surrounding the industrialisation of enabling production technologies and advancing the capability needed for monitoring and controlling process and product quality (Appendices A1 and A2). The choice of operational model, in terms of deployment of the production technology in regional hubs, franchises or hospital settings, implies different transformational impacts on regulatory, business and organisational structures. This is reflected in the last two thematic challenge areas, which are concerned with effective quality management systems and how value is created and delivered (Appendices A3 and A4).



Framed by the scope of the feasibility studies, each thematic area considers challenges related to individual production technologies for emerging product candidate groups, focusing on process-and system-level aspects that reside in the RDM model rather than the product itself, except in cases where product-level interactions impact the wider implementation pathways for RDM. Many of the challenges presented in the cell-factory production platform technology context are generalisable across the 3D-printing technology context.

A summary of the main challenges to realising the benefits of RDM across a range of emerging applications in healthcare is presented.

Challenge Theme 1 Developing the enabling advanced production platform systems and supporting infrastructure for RDM

The fundamental starting point for realising the benefits of RDM lies with further science and engineering advances in manufacturing technologies, looking at how innovative production platform systems are integrated into the wider healthcare system. Overarching issues coalesce around technology and manufacturing capability readiness to accommodate system flexibility, faster low-volume precision, and personalised or customised products and therapies in a local production facility.

In this area, the following significant challenges have been identified.

- Manufacturing technology development to overcome the functional performance capability and productivity limitations of existing bioprocessing and 3D-printing technologies and the constraints imposed by the need for experienced, highly trained personnel and capital-intensive, large footprint controlled environment spaces.

- High up-front capital costs and long timeframes to develop, build and qualify fully automated all-in-one production platform system solutions in advance of phase III clinical trials and accurate market forecasts. Where relevant, this situation presents a significant financial investment risk and disincentive for innovator and manufacturing technology companies.

- A lack of industry standards in the supply chain is a constraint to standardising production platform design, interoperability and assembly for operation under Good Manufacturing Practice (GMP). There is limited industry supply network capacity and capability for responsive supply of standardised manufacturing technologies and critical manufacturing components compatible with a range of raw and starting materials. These factors are a critical barrier to reducing cost, build times, on-site validation requirements and simplifying regulatory review processes for adding additional capacity. The changing economies of scope and scale enabled by RDM and its underlying technologies will impact how existing manufacturing industry supply chains are reconfigured.

- Manufacturing industry and organisational systems engineering skills gaps in the broader manufacturing workforce. This issue will impact innovation and UK competitiveness in the design and development of the future automated production platforms and additive manufacturing systems needed for RDM.

Challenge Theme 2 Development of advanced analytics and characterisation technology to drive automation of enabling production platforms

For many decades, automation has delivered quality and consistency for repetitive processes with centralised manufacturing facilities. In an RDM scenario, companies or health service providers will be responsible for operating and maintaining multiple manufacturing platforms within hospitals, clinics, or even mobile vehicles. This raises the questions: How will the redistribution of manufacturing affect reproducibility, compliance and comparability? How can safety be assured?

For this theme, the following challenges need to be addressed.

- Overcoming the functional capability and performance limitations of existing process analytical and product characterisation metrology. There is a lack of non-destructive, quantitative and rapid analytical methodologies amenable to automation and real-time process monitoring, control and product release. The realisation of RDM is very much dependent on the ability to accurately take measurements in the context of, for example, starting material variation in the case of autologous cell therapies; and multiple cellular, physical-chemical, geometric and mechanical properties in the case of 3D printed products. Current approaches require major technological advances to speed up the process and instruments of measurement, whilst simultaneously allowing easier validation.

- Identifying more quantifiable and robust measures of product quality that link potentially unique personalised or customised product characteristics with function (safety and efficacy). This relates specifically to the question of what to measure. The challenge here is the need to predict the impact of manufacturing process on the clinically relevant product attributes.

- Overcoming technical software hurdles for the acquisition, aggregation, analysis, interpretation and security of multiple sources of data from distributed and interconnected production platforms. This is particularly challenging due to the scale of data, the different types and sources of data that will be generated and the need to integrate and analyse this information. Leading edge developments from other highly regulated industries with similar challenges may be transferrable to applications in healthcare.

Challenge Theme 3 Evolution and synthesis of adaptive regulatory review, governance and approval pathways

RDM and the innovative production methods and digital infrastructures required to enable its implementation presents a challenge to existing and emerging EU regulatory review and governance frameworks (i.e. under ATMP, Pharmaceutical and Medical Device Regulations).

A number of wide-ranging challenges raise new questions related to the features of the production platform technologies and the redistributed model of operation and how current regulatory provisions and decision processes might be applied or influenced.

- Uncertain impacts on product market approval pathways, in terms of meeting safety and quality standards. Production platform technologies present uncertainties related to the regulatory governance of customisable computer-assisted design and manufacture and to closed-system processing in controlled-not-classified spaces. Advances in real-time analytics and characterisation technology, by enabling prospective real-time product release approaches, are likely to challenge conventional end-product testing and batch-centric regulatory paradigms.
- Demonstrating product comparability for approval and deployment of additional manufacturing sites/machines in different geographical jurisdictions presents an unsustainable regulatory burden for the adoption of multi-centre manufacturing models under existing EU frameworks. Likewise, it is unrealistic to expect each site operating a machine for the production and discharge of licensable products to hold a separate manufacturing authorisation.
- Managing legal and regulatory implications for distributing regulatory responsibilities and managing process and product liabilities in the shared chain of custody. This affects the control, management, governance and security of data transferred and shared across sites and individuals. The shortage of regulatory and QP professionals with the necessary cross-sectoral skills and capabilities to administer distributed manufacturing sites and advanced therapies are likely to exacerbate these challenges.

Challenge Theme 4 Developing innovative frameworks for business model and organisational transformation

Much of the existing manufacturing infrastructure is tied to traditional centralised models of operation and economies of scale. Taking a value system perspective, moving to decentralised or RDM models will have a major impact on the way business, organisational and supply chain structures need to be designed and integrated to create, capture and deliver value.

A range of challenges need to be resolved in order to raise the level of institutional readiness for RDM in healthcare.

- New production platform and service system designs are required to assess a suite of future desirable operating scenarios. There is a need for a more informed comparative evaluation of the benefits of RDM to the hospital and the broader healthcare system, compared with conventional centralised provision. If viable routes to market entry are to be established, such an evaluation will need to consider barriers to technology adoption and to deployment of commercial operations in healthcare settings.
- Healthcare infrastructure preparedness is a major issue given the need to minimise disruption to existing infrastructures and healthcare delivery systems, and negotiate solutions that incorporate the operation of new commercial production systems in distributed manufacturing sites. There is a need to overcome potential infrastructure capacity and capability constraints. Also, addressing current gaps in manufacturing skills, capability and training for running routine operations will be essential for managing new ways of working. This is required to ensure and maintain operational quality across multiple, geographically dispersed manufacturing sites and digitally connected responsive supply chains.
- A holistic joined-up value perspective is needed for RDM, which balances the total costs and benefits for the product-service provider, the patient population, the customer and the wider healthcare system. This is in stark contrast to current thinking by manufacturers and health service providers. There is a need to understand and quantify the cost elements for implementing RDM in order to optimise cost structures and define commercially viable economies of scale and scope. However, commercial pathways for RDM will challenge existing conventional medicinal product valuation and payment models. Alternative financial models will be needed that recognise the relative clinical and economic benefits, share risk equitably between multiple stakeholders, minimise payer economic burden and up-front costs and ultimately facilitate affordable patient access.

3 Future Priorities

In order to seize the opportunities presented by RDM, RiHN proposes a bold R&D agenda that incorporates a *whole* healthcare system view of future implementation pathways and wider transformation implications. The RiHN-funded feasibility studies provided evidence of priorities amongst emerging needs, opportunities and challenges involved in taking forward future healthcare research in RDM. The viability of RDM and its successful deployment ultimately depends on the identification of credible platform designs and sound RDM business models. The proposed RiHN R&D agenda presents recommendations across industry, regulatory affairs and business operations.

The priority areas for future R&D can be summarised as follows:

PRIORITY AREAS

- **Development of Automated Production Platform Technologies and Supporting Manufacturing Infrastructures**
- **Development of Advanced Analytics and Characterisation Metrology**
- **Setting the Framework for Regulatory and Governance Pathways**
- **Frameworks for Business Model and Organisational Transformation**

Development of Automated Production Platform Technologies and Supporting Manufacturing Infrastructures

1 To support advances in key manufacturing technologies and their operational performance (including hardware, mechanisation, software, and programmable components)

There is a need to move away from incremental innovation approaches towards the development of high-speed, fully automated, functionally closed, GMP-in-a-box platform systems. Such platforms must deliver the robustness and process capability required to enable the manufacture of licensable CATBTs and 3D-printed products to be replicated with adequate comparability at multiple distributed sites at or near the point of care.

The motivation and skills needed to create these platforms is unlikely to come from any one industrial provider. Rather, the confidence to define the user requirements and the momentum to develop the technology is more likely to come from a pre-competitive community of practice comprised of technology providers on the one hand, and product and process innovators on the other, facilitated by a neutral but motivated 'broker' such as the Knowledge Transfer Network. A focus on alternative business models for sharing the financial investment risk is also needed.

2 To develop industry consensus on need and expectations for the provision of technical standards for manufacturing technologies and critical components

Industry standards will need to focus on building a secure supply chain for compatible manufacturing components, materials and consumables. It is also crucial to standardise data analytics, machine interconnectivity and the real-time acquisition, governance and security of multiple sources of data. Furthermore, effort will need to be directed towards standardising automated production platform design, interoperability and assembly to reduce cost, platform build lead times, on-site validation requirements and to simplify technology transfer processes. Lastly, existing material test methods may not be applicable for the types of products that will be developed via RDM, therefore new and existing standards will need to be reconciled.

3 To develop an innovation-centred, systems-based model for human capital development to support advanced manufacturing technology innovation

There is a requirement to benchmark and leverage learning from other relevant automated production industries to develop responsive programmes and delivery mechanisms to advance systems engineering and programme leadership skills/capabilities. The focus needs to be on developing professionals that can act as production system architects, capable of integrating early and late stage product and process development for CATBTs and 3D-printed medicines.

Development of Advanced Analytics and Characterisation Metrology

4 To advance the development of quantitative, real-time analytical technologies and corresponding data analysis tools
Appropriate in-process controls need to be developed to enable fully automated platforms and provide real-time monitoring and active control of process and product quality. This dictates the need for developing and integrating better automated, real-time process analytics and product characterisation technologies.

5 To progress the discovery and identification of quantifiable measures of product quality
The identification of improved quantifiable measures of product quality is necessary to link product characteristics with function (safety and efficacy) and to in-process controls. This is crucial for enabling interchangeable manufacturing equipment and for demonstrating the ability to manufacture the same product at multiple sites with adequate comparability.

6 To advance data analytics, machine interconnectivity and real-time acquisition, management and security of multiple sources of data
Having all unit operations in a single machine needs further advances in 'big data' technologies that can provide data management systems that can link patient scheduling, manufacturing management systems and chain of custody monitoring within and across multiple distributed production platforms and sites.

Setting the Framework for Regulatory and Governance Pathways

7 To assess the impact that automated production platform technologies will have on product market approval pathways
Engagement with industry and regulatory stakeholders is needed to assess how product safety and the manufacturer's ability to maintain consistent quality will be affected by the unique features of new and emerging innovative, fully automated production platforms that enable closed processing in controlled-not-classified spaces and the potential for real-time product release.

8 To assess the impact that emerging healthcare sector-specific RDM strategies will have on extant legal and regulatory governance frameworks
Industry and regulatory stakeholders must work together to assess how the regulatory and administrative burden for deployment of additional sites/machines and the governance of multi-centre, digitally-enabled manufacturing can be reduced. Also, the implications for distributing the responsibility for quality in the chain of custody needs to be better understood. There must be a robust method for managing the integrity and security of data in the shared chain of custody and how it can be governed across multiple individuals and distributed sites.

9 To extend the UK's ability to provide the relevant specialised regulatory science skills for emerging manufacturing technologies and advanced therapies
There is a need for industry, with appropriate support from academic stakeholders, to lead the development and implementation of a talent plan to secure a sustained supply of regulatory affairs, qualified persons as well as quality and production management professionals. This will capitalise on and translate the UK academic advantage in science and technology research into skilled, experienced personnel to support the regulation and administration of multiple distributed manufacturing sites for the production of a wide range of advanced therapies.

> “The advent of distributed manufacturing and its focus on producing closer to the consumer provides opportunities for SMEs to capture value through last-mile customization, or to completely redefine their business models.”
>
> **WORLD ECONOMIC FORUM (2017)**

Frameworks for Business Model and Organisational Transformation

10 To compile the clinical and economic evidence base

There is a clear requirement to develop models of clinical and redistributed manufacturing processes, and to feed those models with quantitative data that will provide a suite of statistical operational data. This should take into consideration a holistic perspective (technology, infrastructure and through-life material and support) of both cost and benefit data. This will allow for the robust assessment of future system designs and scenarios that will inform RDM investment and adoption in promising applications.

11 Raising the level of organisational capability readiness

As manufacturing shifts location towards service delivery and closer proximity to patients, it is necessary to map the new configuration of industrial roles and responsibilities, new clinical process models, and associated risks and dependencies. Where relevant, the blending of boundaries between public and private entities raises the need to develop exemplar models and test-cases that provide confidence of efficacy. This will provide the basis for understanding the organisational capability and capacity required to further roll-out applications of RDM.

12 To formulate alternative financial reimbursement models

With the disruptive nature of RDM, there is a need to consider alternative reimbursement models. RDM represents a systemic change around the value of the total redistributed system. Pricing and cost models need to reflect this. This should be well understood by manufacturers as the basis for new value propositions and communicated effectively to healthcare payers and policy-makers.

These high-level summary areas are drawn from the more comprehensive and structured ‘system level’ recommendations for future R&D presented in Appendix B. These are categorised by relevant technology context (cell microfactories, 3D printing, and across technologies) and provide detailed guidance for funders and researchers seeking to develop future research proposals. Each of the tables listed in Appendix B presents cross-industry and cross-technology R&D activities needed to address the challenges for transitioning technology and manufacturing readiness levels within the RDM context. Activities are prioritised based on three developmental transition phases, which are colour-coded as **red** (activities for early stage transition – concept and feasibility assessment), **amber** (activities for mid-stage transition – technology development) or **green** (activities for late stage transition – manufacturing development, production and operational deployment). Our approach for the analysis of data and formulation of needs, challenges and future priorities for R&D is presented in Appendix D.

Cell microfactories

3D printing

Across technologies

Summary

RDM has the potential to change the delivery of healthcare products, enhancing the UK's national competitiveness and wellbeing of its citizens. Promising applications of RDM could transform the manufacture of medical devices, pharmaceuticals, biopharmaceuticals and regenerative medicinal products. However, there are key challenges to realising these benefits, including: regulatory standards, new training patterns, social and human factors and quality assurance, as well as the supporting organisational structures and commercial arrangements. The UK's strong science, engineering and commercial base ensures that it is well positioned to compete but, as this White Paper highlights, the complex nature of the challenges underlines the importance of a multi-disciplinary approach, spanning a range of traditionally disparate academic specialisms.

Although RDM is at an early stage of development RiHN recommends that it should be considered as an integrated part of future national manufacturing and life sciences strategy, as well as agendas to transform healthcare service delivery. For instance, RDM presents an opportunity to shape new industrial capabilities, attract international talent to advance new science and manufacturing capability, incentivise investments in infrastructure and exploit the potential of digital innovation; which are all advocated by the 2017 Industrial Strategy for Life Sciences. Future research and investment in RDM will benefit from capitalising on existing strengths and complementary initiatives in the sector that ultimately seek to improve health outcomes for patients and to benefit the economy. These include funding for advanced therapy treatment centres, as well as MMIP's 'Advanced Therapies Manufacturing Action Plan', which sets out actions for further investment in advanced therapies manufacture in the UK and the 'Manufacturing Vision for Pharma', which aims to focus technology and innovation roadmaps towards achieving a step change in new medicines platforms. Furthermore, advances in remanufacturing engineering will present new opportunities for medical products or component parts to be put back into local supply chains for re-use, thus contributing to the circular economy and national sustainability targets.

In the longer-term, RDM is likely to aid the delivery of right-first-time healthcare, enabling access to personalised therapies, bringing the production of medical products closer to where it is needed most – in clinics, emergency departments, military and medical vehicles, or even in areas of conflict or disaster. However, for healthcare stakeholders to realise these benefits, future research must be directed towards solving the challenges and future priorities highlighted in this White Paper. Further effort and investment is required to reach a position where RDM platform systems can deliver medical products rapidly to meet demand, at an affordable or lower cost, and in a more sustainable manner than existing modes of production. Therefore, it is essential to support fundamental research in this area to ensure the UK is positioned at the forefront of RDM in healthcare.

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APPENDIX A – ANALYSIS OF RiHN RESEARCH

A1 Development and implementation of advanced production platform systems and supporting Infrastructures: Needs and challenges

Cell Factory Product Platform Technologies[1]

Cell and Tissue-based Therapeutic (CATBT) Products

NEED

New configurable, portable automated product platform systems that permit production of multiple, vendor/customer specified, licensable products in controlled-not-classified spaces at or near the point of care in multiple dispersed geographical locations, supporting:

- Scale-out of multiple smaller-scale bioprocesses for the manufacture of diverse cell types of varying batch sizes.
- Manufacture of new, lower volume (N=1-100), high-value personalised or precision medicines.
- Responsive 'on demand' or make to order (MTO) manufacture of ready-to-use products.
- Simplified verification/validation requirements and on-site start-up qualification.
- Accelerated product development and launch.
- Repurposing for additional unit operations and future products.

Agile and reliable supply chains for CATBT production system development and supply of critical manufacturing components.

Innovation ecosystem for research and development of advanced manufacturing technologies.

CHALLENGE

Setting the incentives for justifying the high capital cost and investment commitments for building new commercial production platforms and/or facilities before clinical trial results or predicable demand.

Limitations in the relative functional capability of existing core upstream and downstream cell processing and manufacturing technologies.

Bridging knowledge gaps for expanding the scope for automation/mechanisation and integration of enabling technologies into configurable closed-system or portable controlled environments.

Lack of industry consensus on standards for defining requirements for design, assembly and validation of configurable 'GMP-in-a-Box' production platforms and/or portable plants.

Lack of sector-specific standards for configuring and specifying the interoperability functions for connecting upstream and downstream unit operations of the production system i.e. connectivity of the durable, modular, software, programmable and consumable components within/across the functional design space.

Limitations in functional capability of post-production technologies for maintaining the integrity of the finished product at the point of product transfer and delivery of ready-to-use products for administration.

Technical limitations related to reducing or eliminating the consequences of multiple sources of intrinsic/extrinsic variation (biological, technical and operator).

Technical and logistical limitations related to prolonged time-frames for processing and cellular maturation (i.e. to functionally mature cells ready for implantation).

Limited sources of supply for compatible and interchangeable process-contact manufacturing components e.g. most single-use systems are proprietary or custom from single vendors.

Minimising on-site inventories for critical raw materials and consumables required for multi-product MTO operations.

Systems engineering and programme leadership skills and capability gaps for integrating product and process development for manufacture of early and late stage cell-based medicines.

Unclear CATBT industry supply network structure for the design and assembly of production systems, i.e. the machine makers and system integrators who supply the Original Equipment Manufacturers (OEMs).

1 Many of these challenges are generalizable across the 3D printing context.

3D Bio-Printing Technologies[2]

Implantable Tissue Engineered Advanced Therapy Medicinal Products (ATMPs)

NEED

New configurable automated 3D-printing platform systems that permit the design and production of a wide portfolio of licensable 3D-printed products in controlled-not-classified spaces at or near the point of care in multiple dispersed geographical locations that support:

- Manufacture (*ex vivo/in vivo*) of a range of living tissue constructs/organs of varying complexities, anatomical geometries and sizes, ready for implantation.

- High-throughput, MTO manufacture of customised patient-matched products, personalised by geometry and/or constituent cells.
- Ease of changeover between products.

Agile and reliable supply chains for 3D medicines production system development and supply of critical manufacturing components.

Innovation ecosystem for research and development of advanced 3D-bioprinting manufacturing technology.

CHALLENGE

Selecting candidate technologies and a unified printing approach that shows compatibility with a library of materials for fabrication of different 3D functional tissue constructs or organs of varying anatomical geometries and sizes.

Overcoming fundamental limitations in the functional capability of existing underlying 3D bioprinting technologies, related for example to:

- Multi-material printing in the same machine
- Scalability (build size and tolerances) and shape fidelity
- Printing speed, throughput and scope of automation
- Structural and cell distribution resolution
- Aseptic loading/unloading of multiple materials during printing processes
- Intrinsic cellular sensitivity to fabrication materials and processes
- Machine-to-machine consistency
- Fidelity of the CAD-CAM process chain
- Manual post-print processing steps
- Coordinating standards development activities related to engineering and data interoperability of healthcare application-specific 3D-printing production processes.

Limited library of available biocompatible and bioprintable production-grade raw materials.

Lack of suitable post-production technologies that can support the maturation, maintenance and delivery of living 3D tissue constructs of varying geometries and sizes.

Systems engineering and programme leadership skills and capability gaps for integrating product and process development for manufacture of early and late stage 3D medicines.

Unclear 3D-printing industry supply network structure i.e. the machine makers, system integrators and OEMs.

2 Lists specific and additional challenges related to the complexity of each 3D-printed candidate product context.

3D Printing Technologies[2]

Diagnostic Medical Devices

NEED

Fully automated, user friendly 3D-printing platform systems that permit the production of medical devices in non-classified/dedicated spaces in home or primary/ secondary care settings that support:

- Low-volume, MTO manufacture of non-individualised (generic), non-implantable and disposable diagnostic medical devices.
- Easy and safe use by 'non-traditional' device manufacturers in non-specialised facilities.

CHALLENGE

Balancing complexity of device designs with the need to simplify the safe installation and operation of the user- or patient-centric 3D-printing technology in non-specialised/non-dedicated infrastructures and facilities.

Minimising the number of printable parts/sub-assemblies that need to be manually assembled.

Standardising processes for integrating or embedding off-the-shelf electronic sub-assemblies, connections and interfaces (non-printable parts).

Eliminating additional manual post-print processing of sub-assemblies and the finished device.

Eliminating the risk of printer (hardware and software) failure, inadvertent misuse or unauthorised use.

Coordinating the procurement of materials and factory-made non-printable sub-assemblies.

Solid Dosage Forms

NEED

Configurable, portable automated 3D-printing platform systems for re-designing a wide portfolio of existing drug formulations that support:

- Fabrication of solid dosage forms with variable densities and diffusivities, internal geometries, shapes, multiple actives and/or release profiles

and doses tailored to the need of individual and stratified patient populations.

- Scalable, rapid, 'on demand' fabrication of customised solid dosage forms for immediate use in dispersed hospital and compounding pharmacies.

CHALLENGE

Overcoming additional drug-related limitations in the functional capability of existing underlying 3D bioprinting technologies, related for example to:

- Health and occupational hazards (e.g. powder-based 3D printing).
- Tablet surface and morphology imperfections.
- Variable mechanical resistance of tablets.
- Impact and duration of post-print drying steps.

Incompatibility of different material substrates, excipients and active ingredient formulations with each other and with the 3D-printing technology limit stability and efficacy of 3D-printed solid dosage forms and the current application range of the technology.

Limited material choices, colours, and surface finishes available for 3D-printing compared with conventional tablet compression processes.

A2 Development and innovation of advanced analytics and characterisation metrology for coupling product and process quality assurance: Needs and challenges

Cell Factory Product Platform Technologies[3]

Cell and Tissue-based Therapeutic (CATBT) Products

NEED

Advanced quantitative bio-analytic and characterisation metrology tools that support:

- Real-time, in-line or at-line process monitoring and feedback or closed-loop active control of critical process parameters (CPP).
- Non-destructive, sampling and/or rapid measurement of product critical quality attributes (CQA) at the point of release.

Digital technologies that support analytics, integration and management of large data sets across sites to:

- Enable real-time monitoring and adaptive control of multiple CPPs traceable to material and product CQAs.
- Exploit better understanding of the process and the relationship between CPPs, material attributes and product CQAs to accelerate process and product development times.

Relevant skills/training to support improved systems engineering and core data analytical Industry 4.0 capabilities.

CHALLENGE

Bridging from subjective or semi-quantitative metrology to quantitative measurement and characterisation techniques to extend scope for automation of in- or at-line measurements.

Accelerating innovation in smart sensor technology and process analytical technologies to a level that supports automation interconnectivity and integration into configurable production systems to enable in-situ real-time data collection and analysis for in-process control and release testing of multiple products.

Lack of industry consensus on standards for defining capabilities and interconnections for managing acquisition, analysis and interpretation of large multi-parameter 'big data' sets in digital manufacturing operations and supply chains.

Specifying more quantifiable measures of quality (CQAs) that relate to cell identity and link product characteristics to function (safety and efficacy) to enable interchangeable manufacturing and demonstrate the ability to manufacture the same product at multiple sites.

Limitations in the functional capability of current analytical methodologies for characterising the functional identity of therapeutically relevant cell populations at both process and product levels.

Lack of reliable, quantitative potency metrology with sufficient levels of resolution (signal/noise ratio), precision and specificity that can be validated to support in-process, stability and release testing.

Shifting environmental monitoring technology to more rapid, real-time analysis approaches.

Bridging the capability gap for real-time track and trace technology across multi-product manufacturing facilities and supply chains for personalised and precision medicines.

Securing multiple sources of compatible (interchangeable) quality assured analytical/sensor components from different vendors.

Workforce systems engineering and data analytics skills and capability gaps across the digital operations and supply chain infrastructures

3 Many of the cellular level analytics challenges are generalizable to the 3D bioprinting context.

3D Bio-Printing Technologies

Implantable Tissue Engineered Advanced Therapy Medicinal Products (ATMPs)

NEED

Advanced quantitative process analytical/ visualisation and product characterisation metrology that support:

- Real-time, in-line or at-line process monitoring and feedback or closed-loop active control of critical build process parameters (CPP) and material attributes (CMA).

- Non-destructive sampling and/or rapid quantitative measurement of patient-matched 3D-product critical quality attributes (CQA) at the point of release.

New sector and application-specific champions/ leaders for 3D-printing technology and the new era of digitalised computer-assisted design and manufacture operations.

CHALLENGE

Limitations in the functional capability of current analytical methodologies for monitoring and quality control of multi-variate physical, geometric and mechanical properties linked to the detection of design and build errors/flaws in complex 3D structures.

Lack of robust bioanalytical metrology tools for characterising, tracking and visualisation of cells within intact 3D structures and assemblies.

Accelerating innovation in sensor technology and process analytical technologies to a level that supports automation interconnectivity and integration into 3D-printer systems, configurable for in-situ real-time data collection for in-process control and release testing of multiple, customisable 3D-product designs.

Specifying more quantifiable measures of quality (CQAs) that link customisable 3D-printed product characteristics to function (safety and efficacy) or that are predictive of function (product may not be in its final form for implantable products).

Lack of specific industry materials testing standards compatible with unique 3D-printing and post-print processes (e.g. biocompatibility, mechanical testing, etc).

Lack of multi-scale computational and predictive modelling tools limits the ability to define appropriate design limits and tolerances that describe the entire design envelope (i.e. range of each parameter that can be modified) for patient-matched 3D-printed implants.

Shifting sterility assurance to more rapid non-destructive and/or real-time approaches accessible for complex 3D structures with small design features or internal porous microstructures.

Bridging the capability gap for embedding real-time track and trace technology into customisable, patient-specific 3D structures.

Educational and workforce level engineering and digital design skills gaps needed to advance 3D-printing technology applications in healthcare.

3D Printing Technologies

Diagnostic Medical Devices

NEED

Advanced process analytical technologies for real-time, in-line monitoring and control of build processes that support:

- Automated machine quality control and self-diagnostic maintenance, calibration and troubleshooting routines.

- Real-time, in-line process monitoring and feedback or closed-loop active control of critical build process parameters (CPP) and materials attributes (CMA)

Remote quality assurance of individual sub-assemblies by the provider.

CHALLENGE

Defining appropriate design limits and tolerances of multiple individually printed sub-assemblies to error-proof the assembly process and operation of the resulting medical device by non-specialist assembler.

Lack of configurable, intelligent metrology tools for in-situ monitoring of critical machine operational performance indicators limit the ability to detect malfunctions and support self-diagnostic, maintenance, calibration and troubleshooting routines.

Standardising the acquisition of patient-matched machine and process QC data to provide operational transparency and simplify analysis, interpretation and supervision of multiple 3D-printers by remote, trained healthcare providers.

Lack of industry standards for defining the capabilities and interconnections for managing the transfer of data between individual patient-matched 3D-printed diagnostic medical devices and remote clinical healthcare providers.

Solid Dosage Forms

NEED

Advanced quantitative process analytical/ visualisation and product characterisation metrology that support:

- Real-time, in-line or at-line process monitoring and feedback or closed-loop active control of critical build process parameters (CPP) and material attributes (CMA).

- Non-destructive, high-throughput, quantitative measurement of multiple, customisable solid dosage form critical quality attributes (CQA) at the point of release.

CHALLENGE

Specifying more quantifiable measures of quality (CQAs) that link solid dosage form characteristics to function, for instance, related to safe and efficacious oral delivery of the API(s) (e.g. purity, structural integrity).

Lack of robust, quantitative characterisation metrology with sufficient resolution, precision and specificity to detect variation/errors in physical, chemical, geometric and mechanical properties of small heterogeneous solid dosage forms.

Lack of multi-scale computational and predictive modelling tools limits the ability to define appropriate design limits and tolerances that describe the entire design envelope for customised solid dosage forms.

Lack of validated characterisation metrology to support accelerated stability trials of solid dosage forms with multi-API formulations and complex release kinetics.

Lack of industry standards for defining the capabilities and interconnections for managing the transfer of data between the pharmacy, patient and the clinician, limiting real-time options for adjusting solid dosage form designs to prescription or to clinical outcomes.

A3 Evolution of frameworks for predictable and viable regulatory and governance pathways: Needs and challenges[4]

Cell Factory Product Platform Technologies

Cell and Tissue-based Therapeutic (CATBT) Products

NEED

Evolution and synthesis of adaptive regulatory review, governance and approval pathways that:

- Accelerate the procurement and licensure of new manufacturing capacity. Supporting innovative change control and technology transfer procedures that allow rapid deployment of CATBT production platforms at or near the point of care in different jurisdictional geographical markets, proportionate to the spectrum of risk.
- Harmonise the way regulatory standards and building codes are implemented and interpreted across different geographic areas and markets.
- Deliver cross-border legal frameworks and regulatory provisions that recognise both the product and service elements of RDM approaches and the obligations of multiple participants involved in the production and supply chain.
- Support transition to innovative real-time process control and product quality assurance approaches, applicable to 'on demand' manufacture and release of patient-centric products that can be personalised to individuals or stratified patient populations.

Skills and knowledge ecosystem for specialist cross-sector regulatory and QP professionals.

CHALLENGE

High evidentiary regulatory burden and timeframes associated with demonstrating product comparability for approval and deployment of additional, follow-on manufacturing sites/machines in different jurisdictional geographical regions (pre- and post-MAA).

Impracticalities and sustainability of the need for each host site operating a machine for the production and discharge of CATBT products to hold a separate manufacturing authorisation.

Delineating the regulatory and legal obligations of the MAA licence holder and the host sites (hospital/franchise) for traceability and record keeping in the chain of custody throughout each product's lifecycle.

Impracticalities and sustainability of the requirement for the physical presence of a QP at each host site.

Sustaining consistent governance oversight of manufacturing and QC steps across multiple sites/machines.

Maintaining consistent levels of training/competency to ensure compliance across all host sites.

Delineating the scope of product and process liabilities in the shared chain of custody.

Uncertainty related to the impact of Brexit on the future regulatory environment and consequences for UK manufacturing and supply chains.

Standardising automated platform design and validation criteria for producing multiple licensable products under divergent geographical clinical, manufacturing and supply chain regulations.

Uncertainty related to regulatory acceptability of closed-system processing in controlled-not-classified spaces.

Incompatibility of real-time release testing approaches with batch-centric regulatory paradigms.

Impracticalities of managing retained/reference samples for complex individualised and MTO products.

Unresolved questions around regulatory/legal governance of the digital infrastructure required for the control, management and protection of data across multiple sites/machines.

Minimising concerns related to unauthorised production, off-label prescribing, adulteration or mix-up of treatment regimens.

Additional compliance complexity related to the in-situ, 'on demand' personalised packaging and labelling of multiple individual products.

Long-term effects related to the disposal of single-use components used in bioprocessing.

Skills/knowledge gaps for provision of specialised roles in the regulation and administration of advanced therapies and manufacturing facilities.

4 Based on constraints under the scope of the current regulatory frameworks; where the main novelty resides in the process of manufacture rather than the product itself. Generic product-specific challenges or those related to precision medicine or to pre-clinical or clinical trials are therefore not considered.

3D Printing and 3D Bio-Printing Technologies[5]

- Implantable Tissue Engineered Advanced Therapy Medicinal Products (ATMPs)
- Diagnostic Medical Devices
- Solid Dosage Forms

NEED

Evolution and synthesis of adaptive regulatory review, governance and approval pathways that:

- Accelerate the procurement and licensure of new manufacturing capacity. Supporting innovative change control and technology transfer procedures that allow rapid deployment of 3D-printer production platforms at or near the point of care in different jurisdictional geographical markets.
- Deliver cross-border legal frameworks and regulatory provisions that recognise both the product and service elements of RDM and define the obligations of the designer, the equipment the producer/owner/supplier, the manufacturer and the consumer within the liability spectrum.
- Support innovative real-time quality assurance approaches applicable to unique 3D-printer build processes and to divergent classes of 3D-printed products that can be customisable in the 'on demand' computer-aided design and manufacturing process.
- Support computer-aided design and manufacture of 3D-printed products proportionate to the specific product type, classification and risk to the patient, e.g. ranging from active implantable devices or medicinal products, drug delivery systems and non-active implantable devices to non-implantable devices.
- Support the delivery of sustainable eHealth and data protection systems.

CHALLENGE

Absence of distinct 3D-printing legislation raises uncertainties/ambiguities related to delineating the extent existing regulatory regimes/ standards and emerging regulatory reforms apply to the 3D printing, post-print processes and 3D-printed products.

Impracticalities and sustainability of the implied need for each host site operating a 3D printer for production and discharge of 3D-printed devices/ products to hold a separate manufacturing authorisation.

Current IP/security methodologies and legal systems are not appropriate for digital networks and ways of working required for 3D printing.

Minimising product liability exposure risks related to the control of customisable CAD/CAM processes and the involvement of multiple participants in the production and supply chain.

Uncertainty related to where the limits of regulatory authority lie for the design and manufacture of customisable 3D-printed products in hospital and pharmacy settings.

Impracticalities of managing retained/reference samples for complex, customised ('batch of one') 3D-printed products.

Unique build processes and multiple design variations of customisable 3D-printed products render conventional design process verification and validation approaches difficult to apply.

Establishing acceptable procedures for oversight of post-print finishing processing and/or manual assembly of the finished 3D-printed device by untrained, non-specialists in home settings.

Unifying Quality Systems across industry GMPs (Pharma, Medical Devices, ATMPs) to direct, control, and coordinate the quality of multiple 3D-printed product lifecycles.

Minimising regulatory concerns related to unauthorised printing, illicit use of raw materials and potential for mix-ups in patient drug or dosing treatment regimens.

Establishing the regulatory scope for combining 3D-printing with conventional drug manufacturing lines for producing a wider range of compounds during drug development and clinical trial.

5 Lists additional and specific challenges related to the regulation of 3D printing.

A4 Developing innovative frameworks for business model and organisational transformation: Needs and challenges[6]

Cell Factory Platform, 3D Bio-Printing and 3D Printing Technologies

- Cell and Tissue-based Therapeutic (CATBT) Products
- Implantable Tissue Engineered Advanced Therapy Medicinal Products (ATMPs)
- Diagnostic Medical Devices
- Solid Dosage Forms

VALUE PROPOSITION	NEED	Formulation of a compelling value proposition based on the design and integration of the product (core platform technology and accompanying modular, digital and consumable components) and service offering (compliance & security components). Maximising the creation, capture and delivery of value for customers (healthcare providers, payers and users) and patients in primary and/or secondary care settings.	
	CHALLENGE	Identifying the most promising production system design and options for configuring the mode of operation (e.g. via hub, franchise, hospital) that delivers maximum value-add (*the 'sweet spot' for converting the value proposition into sustainable revenue streams in the RDM landscape*). Identifying patient populations and candidate product group profiles where development efforts should be targeted and economies of scope can be leveraged to maximise patient benefit, healthcare system benefit and reimbursed price potential (*the solution space*). Identifying viable market channels and predicting the scale of target customer and market demand for the enabling production technologies.	
CUSTOMER INTERFACE	NEED	Creation of customer interfaces and ways of working to establish viable routes to market entry and create pathways to adoption and delivery of value to customers and patients.	Digitalisation and integration of vertical and horizontal value chains to optimise collaborative relationships.
	CHALLENGE	With little heritage of experience, the level of implementation challenge to local, regional and national healthcare systems and traditional professional constructs introduces significant barriers to adoption of manufacturing technologies and commercial manufacturing operations in hospital settings. Forming long-term collaborative partnership and transactional arrangements with the health service provider to build a viable business model for the hospital and embed	the required capacity and supply chains for commercial RDM operations (i.e. via hub, franchise or hospital). Overcoming healthcare system barriers to the implementation and delivery of customer-centric servitisation strategies. Building and maintaining digital trust in continuous data flows that result from vertical and horizontal value chain networks.
VALUE CONFIGURATION	NEED	Configuration of the value system to deliver the value proposition and maintain customer interfaces.	Development of the business-critical capabilities and partnership networks needed to transform the organisational capability readiness of the supplier (equipment provider) and the customer (as the manufacturer at the host site) for carrying out the activities necessary for creating and delivering value.
	CHALLENGE	Existing levels of institutional readiness in healthcare limit opportunities for standardising technology transfer methodologies. Bridging existing physical infrastructure constraints/gaps to raise the level of facility readiness at distributed host sites for installation, set-up and operation of supplied commercial cell micro-factory or 3D-printing production systems. Bridging digital infrastructure constraints/gaps to raise the level of interconnectivity within existing healthcare infrastructural networks and between the central and host site to aid delivery of servitisation strategies. Addressing the core human resource capability and capacity constraints/gaps	at distributed host sites, including the need for manufacturing technicians/operators and essential personnel (QP, production managers, QC controller and responsible persons). Minimising the level of organisational change or disruption to existing treatment algorithms and healthcare delivery processes. Minimising the administrative/regulatory burden and exposure to regulatory compliance risk at each host site in the network. Establishing centralised training centres (i.e. with identical equipment/facility configurations), providing access to standardised operational and compliance training for operators/technicians running routine manufacturing operations at distributed host sites.

6 Several business model configurations are possible depending on the operational model and the level of servitisation and customisation. Each configuration may raise different challenges. The following table considers challenges that are generalisable to both cell factory and 3D printing contexts. Specific challenges related to the choice of cell lines, the use of an intermediate cell banking step or co-development of companion diagnostics are not considered.

FINANCIAL DESIGN STRUCTURE

NEED

Cost structures that support commercially viable economies of scale and scope, in line with the demonstration of value and market growth.

Build innovative and flexible payment, financial and EU market access models that:

- Recognise and translate customer value (clinical and economic) into sustainable and highly profitable incoming revenue streams.
- Balance risk and financial exposure of payers with differing value/cost drivers across multiple geographies.
- Enable patient access to affordable new therapies and minimise economic burden of patients and healthcare providers.

CHALLENGE

Defining realistic total cost/benefit thresholds:

- Dearth of information for monetising the fixed/variable costs of operational business models, making it difficult to predict the investment needed for translation.
- Unpredictable revenue, cost and efficiency gains related to the servitisation elements of the value creation process.
- Uncertainties related to valuing (£) and demonstrating long-term clinical and economic impact/benefits (added value) of the product-service offering to the patient population, to the hospital and the broader public and private healthcare systems.

Unpredictable rate and volume of market penetration/expansion weakens strategies for mitigating high financial investment risk in capital equipment acquisition or facility build.

Rationalising reimbursement and pricing strategies, in terms of the holistic value framework for the patient population and the healthcare system at local, regional and national levels.

Geographical variation in the relative importance of clinical and economic considerations and type of health economic framework applied.

Added market access and economic uncertainties related to the evaluation of low volume personalised, customised and potentially curative medicines and the requirements for accompanying interventional procedures.

Dispersed ownership of the chain of custody challenges conventional reimbursement and payment frameworks.

APPENDIX B – PROPOSED RESEARCH AND DEVELOPMENT AGENDA FOR REDISTRIBUTED MANUFACTURING

B1 Science, Research & Development Priorities for Redistributed Manufacturing

Develop and Implement Advanced Production Technologies and Manufacturing Infrastructure

I1 Building the manufacturing infrastructure and workforce

	Translate and capitalise on learning from other automated production industries (e.g. automotive, electronics industries) to develop a talent plan for securing the systems engineering and programme	leadership skills and capabilities needed for integrating early and late stage product and process development programmes for CATBTs and 3D-printed medicines.
3D	Establish an industry group to map the global 3D-printer technology supply network (the machine makers, system integrators and OEMs) to identify the capacity/capability of the industry and evaluate the maturity level of the systems that may be integrated into future platforms solutions	for healthcare applications. The aim is to determine the technology gaps and identify UK strategic priorities with respect to building robust supply chains and long-term 3D-printing manufacturing capability in the UK.
3D	Widen industry engagement with relevant standards-setting organisations to extend and coordinate the development of specialised technical standards for defining requirements and specifications for the design, engineering	and interoperability of autonomous 3D-printer production platforms (and associated test/validation procedures) for relevant sector-specific processes and applications.
	Establish an industry group to map the global Cell & Tissue Based Therapy (CATBT) industry supply network structure (the machine makers, the system integrators and OEMs) to identify the capacity and capabilities of the industry for the design	and assembly of CATBT platform production systems. The aim is to determine the technology gaps and UK strategic priorities with respect to building a robust supply chain and long-term RDM capability in the UK.
	Establish industry working group with component suppliers to identify opportunities for standardisation, improving compatibility between different vendors and shortening lead times for critical production	components (e.g. single-use devices and connectors). The aim is to create an agile and reliable digital supply chain to minimise on-site inventories and ultimately reduce facility footprints.

I2 Advancing production system technology readiness

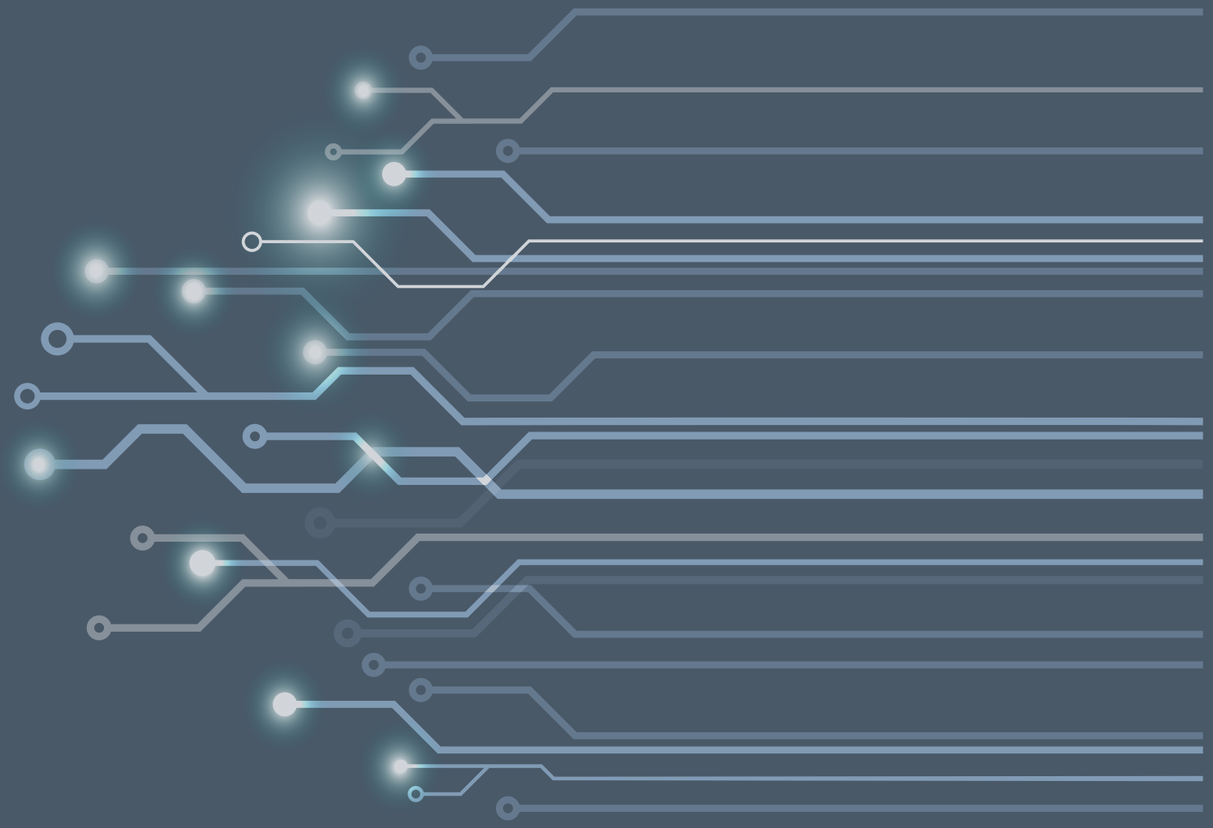
	Establish a multinational working group to explore the equivalency of the UK/EU clinical, manufacturing and supply chain regulatory (and building) standards and the links to the clinical constraints for distribution and deployment of	manufacture to each region. The aim is to provide the technical basis for deriving unified guidance to support the design and development of production platform systems that can be specified for transfer and deployment in multiple geographical locations.
	Drawing upon the regulatory equivalency exercise, establish a pre-competitive community of practice (comprising technology providers and product/process innovators) to identify common user requirement specifications (URSs) as a technical basis for the rational design of automated production platforms for the manufacture	and delivery of CATBTs. The aim is to provide a platform for knowledge transfer and the motivation and skills needed for the collaborative development of these production platform technologies and their supporting manufacturing technology supply chains.
	Cross-industry foresight review of the high-value manufacturing innovation landscape to identify and evaluate opportunities for advancing the functional capability maturity and scope for automation/mechanisation and integration of core upstream	and downstream cell processing and manufacturing technologies. The aim is to identify the mainstream, maturing and emerging technologies that can be prioritised or monitored for future application in cell micro-factory production systems.
3D	Drawing upon the regulatory equivalency exercise, establish a pre-competitive community of practice (comprising technology providers and product/process innovators) to identify common user requirement specifications (URSs) as a technical basis for the rational design of automated, 3D-printing production platforms for the	manufacture and delivery of 3D-printed products. The aim is to provide a platform for knowledge transfer and the motivation and skills needed to advance the functional capability maturity and scope for automation/mechanisation of candidate 3D-printing platforms.
3D	Advance the interoperability of 3D-bioprinting technology in specific areas that support automation and integration of aseptic cellular	processing steps and/or cell delivery sub-systems into configurable production systems to improve user interfaces.
3D	Extend material science enabled advances in the discovery, design and engineering of chemically defined synthetic material and biomaterial	(bioinks) substrates to expand the library of stable biocompatible and printable production-grade materials.
3D	Advance the capability and interoperability of the computer-aided design to manufacture chain (CAD-CAM step). The aim is to provide better control of multiple translation and compilation steps and reduce the potential for errors in design	input translation, while providing simplified and easier to use software that can be configured or customised for application-specific design models and printing processes.

I3 Advancing post-production system technology readiness

Advance the functional capability maturity of post-production technologies to extend opportunities for automation and process integration, focusing on scalable closed-system technologies for detecting and selectively eliminating unwanted cells, fill and finish technologies and standardised technologies for product transfer, delivery and administration.

Advance the scalability and functional capability maturity of post-production bioreactor technologies in specific areas that accommodate prolonged time-frames for complex cellular-material remodelling and maturation and support the maintenance and delivery of living 3D tissue constructs of varying geometries and sizes.

Advance the functional capability maturity of post-production technology in specific areas that support automation and process integration of additional post-print treatment processes (such as drying steps) into configurable 3D-printing production systems for solid dosage forms.



B2 Priority Research & Development for Analytics and Metrology Science for Redistributed Manufacturing

Analytics and Metrology Science Research & Development Priorities for Redistributed Manufacturing

I4 Building digital Quality Assurance infrastructures

Extend industry engagement with relevant standards-setting organisations to determine the applicability of current international standards and EU pharmacopoeia material test methods to 3D-printing processes (e.g. biocompatibility, mechanical testing). The aim is to explore state-of-the-art and identify the required actions to reconcile standards applicability gaps that relate to real-time release testing approaches and to the customisability and unique build processes of 3D-printed products/devices, including post-print processes such as cleaning, finishing and sterilisation.

Establish a working group, in collaboration with relevant measurement organisations, to consider the technical requirements for development and specification of machine calibration/reference materials, reference standards for analytical test methods and data reference sets for data analysis, presentation and interpretation. Aim is to develop a framework for comparative analytics and the provision quality standards across the RDM network.

Drawing on the quality standards development exercise, explore strategies for implementation of an external, centralised QA scheme/service based on, for example, the periodic introduction of positive and negative quality control and/or calibration material into distributed micro-factory platform manufacturing processes. Aim is to enable trending and proficiency testing of manufacturing and analytical performance (independent of product lots) to confirm that processes and methods remain in a state of operational control across multiple sites.

Drawing on the quality standards development exercise, explore strategies for implementation of an external, centralised QA scheme/service based on, for example, the periodic introduction of standardised fabrication protocols/reference materials into distributed 3D-printer production systems. Aim is to enable trending and proficiency testing of design and build performance across multiple 3D-printer platforms and sites.

Establish a working group, in collaboration with the relevant standards-setting organisations, to consider the challenges for standardising the interoperability of data and machines, the use of data to support manufacturing decisions, governance in the digital environment and model performance validation. Aim is to develop a sector-specific view and consensus on requirements for developing standards to encourage collaboration and data sharing in RDM supply chains.

I5 Advancing in-line monitoring, process characterisation and control technology readiness

Review the high-value manufacturing innovation landscape in other relevant sectors (e.g. pharma/biopharma/food industries) to identify opportunities to transfer best practice and/or exploit advances in digital technologies, sensor devices, data analytics, data integration and management across production platforms and the RDM value chain.

Investigate the application of Quality by Design (QbD) methodologies to evaluate the relationships between process parameters, material attributes and product properties for representative case studies. The aim is to establish 'generic-level' critical process parameters (CPPs) that should be monitored during production and to define the metrics and in-process analytical tools that apply and that can be extended to specific cell-factory applications.

Investigate the application of QbD methodologies to evaluate error/failure modes and the relationships between process/build parameters, the material attributes and the final product properties in representative case studies. The aim is to establish the 'generic-level' CPPs and critical material attributes (CMAs) that should be monitored during production and to define the metrics and in-process analytical tools that apply and that can be extended to specific 3D-printing applications.

Develop enhanced multi-variate data mining and advanced pattern recognition analytics capability to facilitate identification of CPP relationships with critical quality attributes (CQA). Aim is to provide the basis for the design and development of closed-loop control systems.

Advance the development of real-time, non-destructive process analytical technology (PAT) and non-invasive, quantitated imaging technologies that can provide the basis for precise real-time monitoring and feedback control of CPPs, are compatible with in-line automation and are immune to scalar effects. Aim is to transition from end product testing and tightly controlled CPPs and CMAs to automatic real-time testing and flexible CPPs to respond to input variation.

Establish a collaborative working group with OEMs to specify and advance the functional capability of in-situ sensor and in-process analytical and data acquisition technologies that can support real-time monitoring and closed-loop control of multi-variate physico-chemical, geometric and mechanical properties. Aim is to enhance the ability to detect and mitigate build errors/defects and reduce or eliminate the need for post-print processing steps.

Establish a collaborative working group with OEMs to specify and advance the functional capability of biosensor and in-situ real-time process bioanalytical and quantitated imaging technologies for tracking and visualisation of cells and contaminating biological organisms within intact 3D tissue construct structures.

I6 Advancing product characterisation, CQA testing and measurement technology readiness

Pre-competitive benchmarking activity to extend opportunities for specifying more quantifiable measures of quality (CQAs) that link cellular product characteristics to function (safety and efficacy). The aim is to provide the basis for developing the industrial metrology needed to enable interchangeable manufacturing and enhance the ability to manufacture the same product at multiple distributed sites.

Pre-competitive benchmarking activity to extend opportunities for specifying more quantifiable measures of quality (CQAs) that link 3D-printed product characteristics to function (safety and efficacy) or are predictive of function (*product may not be in its final form when implanted*) for representative cases.

Advance the development of sensor and control devices that can be incorporated or embedded into ex vivo 3D niches to add new levels of functionality to 3D structures and provide real-time monitoring and remote control of niche components within 3D assemblies (e.g. remote actuation or active modulation).

Develop in-situ cell-specific sensor platforms (disposable/reusable) with plug-and-play options for different cell types, which can be applied to the real-time in-line measurement of CQAs at cellular and sub-cellular levels. The aim is to extend opportunities for predicting the quality of cellular starting materials, intermediates and drug substances.

Develop robust, simplified and quantitative product characterisation metrology with enhanced levels of resolution (signal/noise ratio), precision and specificity. The aim is to provide the basis for the initial development of a panel of 'For Information Only' tests that can be validated and transitioned to support in-process control, stability testing and product release and, where possible, can be standardised across product groups.

Advance the development of monitoring subsystems that allow real-time and high resolution determination of drug dosing.

Explore direct (e.g. introduction of labelling agent into cells) and indirect (e.g. introduction of reporter gene) labelling and molecular imaging modalities as a basis for the development of real-time cell tracking capability amenable to automated visual inspection, both in-process and after clinical administration.

I7 Advancing assurance of manufacturing quality

Advance the development of next generation multi-scale computational and predictive modelling tools. By linking multiple design, manufacturing and materials attributes, the aim is to enhance understanding of 3D-printing error budgets and provide the ability to predict outcomes and define appropriate design limits and tolerances (i.e. for verifying that the finished product meets the design inputs).

Investigate new methodological approaches for building standardised design control models for customised 3D-printed devices to enable design verification and design validation steps to be incorporated into the overall design and manufacturing process. The aim is to adapt approaches from GMP and existing bracketing/ matrixing approaches to develop standardised 'worst-case' performance challenge methodology for addressing the numerous design parameters that can be customised based on user needs (i.e. accommodating design envelopes with an infinite number of design variants).

Explore and develop predictive modelling approaches and methodologies as surrogates for design validation of customisable 3D-printed devices and for modelling future states of the device, such as growing tissues or material degradation under challenge conditions (e.g. Finite Element Analysis for predicting mechanical performance).

Advance the development and application of multi-variate statistical process control and other statistical projection concepts and techniques for real-time monitoring of agile production systems and for situations where products are manufactured in small batch sizes or can be customised within process.

Explore and develop a standardised mechanism for testing the consistency of 3D-printing builds, for instance, design and manufacture of representative, standardised constructs or coupons with each build to detect build variations.

Advance the development of non-destructive methodologies for testing the efficiency of post-manufacturing cleaning and sterilisation processes and their impact on the fidelity of the final manufactured device.

I8 Advancing data management and information technology readiness

Develop generalisable process maps of all data sources across the process/product workflow for representative RDM case studies and digital scenarios. The aim is to identify the touch-points where data is collected and exchanged across the vertical and horizontal value chain to provide the basis for a data and information technology asset requirement and capability gap analysis.

Drawing upon the digital asset and capability gap analysis, establish a working group to explore the information technology and Industry 4.0 landscape. This is to identify and evaluate opportunities to exploit existing and emerging digital platforms and sensor-enabled software solutions for managing and securing the real-time acquisition, aggregation, analysis and interpretation of multi-parameter data streams from manufacturing processes and workflows across multiple sites. The aim is to map out an Industry 4.0 strategy that can improve business processes and build digital trust.

Advance the development of scalable and compliant product serialisation technology (e.g. RFID, watermarking technologies) that can be integrated into cell micro-factory and 3D-printer production lines to provide a holistic approach to product tracking and traceability across supply chains. The aim is to address the need for real-time visibility into where a specific individual product physically resides in the downstream supply chain in order to recognise counterfeit situations, identify expired products and perform targeted recalls, i.e. moving away from batch-centric materials management.

B3 Regulatory Science Research & Development Priorities for Redistributed Manufacturing
Setting the Framework for Regulatory and Governance Pathways

R1 Developing a viable regulatory strategy

	Establish an industry group, with appropriate support from academic stakeholders, to lead the development and implementation of a talent plan to secure a sustained supply of regulatory affairs, qualified person and quality/production management professionals. The aim is to capitalise	on and translate the UK academic advantage in science and technology research into skilled, experienced personnel to support the regulation and administration of multiple distributed manufacturing sites for the production of a wide range of advanced therapies.
3D	Drawing parallels with relevant custom-made device, Hospital exemption and 'Specials' regulatory pathways, establish a working group, with support from appropriate stakeholders, to identify where the limits of regulatory authority might apply to the product and service based elements of RDM.	The aim is to delineate between 'routine' industrial manufacture and 'non-routine' manufacture of customisable 3D-printed devices in hospital settings and the regulatory/liability distinction between products that are 'placed on the market' or 'put into service' using representative case examples.
	Establish an industry group, with support from appropriate stakeholders, to consider and develop guidance on the definition of closed-systems and the acceptability of closed-system processing in low-grade or controlled-not-classified spaces. As a key enabler for simplifying operating costs	and facility design/re-engineering, commissioning and qualification, the aim is to test a new regulatory strategy where the host facility is treated as equipment for purposes of qualification and validation.
3D	Drawing upon representative 3D-bioprinting case examples, engage with appropriate stakeholders to identify the regulatory/liability boundaries between	the customisable manufacturing process and the practice of medicine to define the specific activities that lie outside the bounds of regulatory jurisdiction.
3D	Drawing upon representative 3D-printing case examples, engage with appropriate stakeholders to identify the regulatory/liability boundaries between the customisable manufacturing process and	practice of pharmacy to delineate the distinction between compounding and manufacturing and to define specific activities that lie outside the bounds of regulatory jurisdiction.
3D	Establish a working group to delineate the extent to which existing regulatory regimes (medical devices, pharma, ATMP) and emerging reforms (e.g. new EU MDD, EU Falsified Medicines Directive, General Data Protection Regulation) apply to the 3D-printing machine, the controlling software and process	(CAD to CAM chain), the component materials and the 3D-printed product itself. The aim is to determine the logic and scope for provision of distinct 3D-printing legislation and for the early development of standards and guidance.
3D	Leveraging learning from recent approvals (e.g. Aprecia Pharmaceuticals ZipDose® Technology), establish a working group to explore the regulatory scope for combining 3D-printing with conventional	drug manufacturing lines to extend the flexibility in the production of a wider range of solid dosage forms during clinical trials.
	Drawing on emerging solutions in the precision medicine space, engage with appropriate stakeholders to explore the legal, ethical and regulatory challenges for the governance of the implied digital assets and infrastructures	required for the control, management and protection of data that may be transferred and shared across multiple sites, stakeholders and machines in the RDM operational context.
	Engage with appropriate stakeholders to consider and explore the scale of uncertainties and opportunities related to the impact of Brexit on the future UK regulatory and reimbursement environment	and consequences for UK manufacturing and supply chains in the context of RDM. The aim is to realise opportunities to influence any national plans for adapting relevant regulations in the UK.
	Establish an industry-wide initiative to explore solutions for recycling, energy reuse or greener manufacturing and disposal strategies to meet	the expected increased reliance on the use of single-use components in bioprocessing.

R2 Transforming requirements for demonstrating product and process quality control and assurance

	Extend hypothetical case scenarios to explore and test alternative, streamlined and rational approaches for demonstrating product comparability. As a basis for discussion with Competent Authorities, the aim is to develop proposals that could support regulatory	approval for the addition of new manufacturing sites/ machines and for transferring multiple manufacturing processes and analytics to different geographical regions (pre- and post-MAA).
	Extend hypothetical case scenarios to explore and develop alternative manufacturing licensing models that consider new risk-based categories of manufacturing authorisation and inspection, which recognise the use of automated, closed-system production platforms and the customisable	nature of processes/products. As a basis for discussion with Competent Authorities, the aim is to develop proposals that envisage host sites becoming satellite manufacturing sites under a main central hub licence holder.
3D	Review the CMC and design control requirements that currently apply to the conventional manufacture of combination ATMPs and Medical Devices under existing EU regulatory frameworks. The aim is to draw on hypothetical case scenarios to explore their	applicability to 3D-printing and identify the actions required to reconcile the elements that relate to the customisability and unique build processes of 3D printers, including unique post-print processes such as cleaning, finishing and sterilisation.
	Drawing on the CMC review, extend hypothetical case scenarios to investigate the application of continuous quality verification methods as an alternative process validation approach.	In line with the real-time product release philosophy, the aim is to develop proposals as a basis for discussion with Competent Authorities.

Review the GMP/QS requirements that currently apply to the conventional manufacture of Medical Devices and combination ATMPs under existing EU regulatory frameworks. The aim is to design and develop a unified and streamlined Quality System that integrates the operational provisions for the manufacture of both the medical device and cellular constituent parts of 3D implantable products (i.e. for manufacturers making both constituent parts in the same facility).

Drawing upon the GMP/QS review, engage with appropriate stakeholders to explore how the principles of GMP and the associated inspection/audit frameworks can be made more applicable to the parallel, aseptic manufacture of multiple cell-based products in automated, closed-system production platforms that can be operated in 'controlled-not-classified' room environments.

Extend hypothetical case examples to develop and structure alternative approaches for justifying planned derogations from the requirements to hold retained and reference samples, for instance, in cases where the individualised or customised and MTO ('batch of one') nature of products make these requirements impractical or unfeasible. The aim is to develop proposals as a basis for discussion with Competent Authorities.

Establish an industry group, with support from appropriate stakeholders, to consider the translational level challenges for navigating away from batch-centric regulatory paradigms towards future pathways for regulatory approval of real-time release testing approaches.

R3 Transforming procedures for governance in the chain of custody

Develop generalisable process maps to identify all the hand-off points in the chain of custody for representative hypothetical case scenarios to delineate the scope of product and process liabilities in the legal framework for the commercial manufacture of goods in hospital, franchise or home settings. The aim is to explore the transactional arrangements and opportunities to reduce or eliminate the liability exposure of multiple participants within the production and supply chain.

Extend the process mapping exercise to advance understanding of the additional regulatory/legal risk exposures related to data control, management and protection across multiple machines that incorporate the use of configurable or customisable, controlling software (CAD-CAM chain) in the printing process.

Establish a working group to explore options for streamlining the chain of custody for traceability and release of goods, drawing on the process maps for hypothetical cases to delineate the regulatory/legal obligations of the MAA licence holder and the host sites. The aim is to consider how an equal level of confidence in the quality and pharmacovigilance of released goods can be achieved through remote monitoring by centralised or regional QPs and to develop proposals as a basis for discussion with Competent Authorities.

Drawing on the process mapping exercise, establish a working group to consider and test hypothetical scenarios that can lead to failure modes in the chain of custody. The aim is to advance understanding of the risks related to unauthorised production, illicit use of raw materials/reagents, the potential for mix-ups in patient drug or dosing treatment regimens or the potential for off-label prescribing. This will provide the basis for assessing the severity, probability of occurrence and ability to detect risks across different business operational scenarios that leverage distributed cell-factory and 3D-printing production platforms and to identify opportunities to build in tamper-proof strategies.

B4 Operational Research & Development Priorities for Redistributed Manufacturing Frameworks for Business Model and Organisational Transformation

O1 Constructing a quantifiable value proposition for market access

Establish a working group to understand and identify disease areas and addressable target patient populations where economies of scope (the degree of product flexibility) can best be leveraged by the features of the cell micro-factory platform technology, accounting for future trends towards personalised and precision medicine. The aim is to provide a therapeutic framework for targeting platform-compatible CATBT product groups (number and type of products per facility) with sufficient value release for innovator companies, based on expected clinical benefits of each product candidate.

Establish working group to explore the number and location of potential treatment centres to identify the market channels where economies of scale (the degree and proximity of distribution) and business advantages can best be leveraged by the attributes of RDM. The aim is to provide a market framework for strategically targeting the predominant prescribers, key opinion leaders (KOL) and payers in each channel where the CATBT products will be used most and where they will realise greatest revenue potential, considering the differing value propositions of the public NHS system and the private healthcare networks (civilian and military).

Establish a working group to understand and identify the therapeutic areas and addressable target patient populations where economies of scope can best be leveraged by the features of the 3D-printing technology and service offering, accounting for the patient/product benefits conferred by the level of customisation and personalisation. The aim is to provide a therapeutic framework for targeting 3D applications with sufficient value release based on expected clinical benefit compared with current standard of care, including prosthetics, implants, fabricated tissues and organs, solid dosage forms and medical devices.

Establish working group to explore the number and location of potential treatment centres to identify the market channels where economies of scale and the business advantages can best be leveraged by the attributes of RDM. This must consider the potential need for complex interventional surgical procedures associated with some implantable devices. The aim is to provide a market framework for targeting the predominant prescribers, KOLs and payers in each channel where the 3D devices/products will be used most and where they will realise greatest revenue potential, considering the differing value propositions of the public/private healthcare networks (civilian and military), specialist pharmacies and the pharmaceutical manufacturers.

Develop a framework to broadly categorise and describe the potential clinical and economic value of expected patient benefits (e.g. magnitude of added value in terms of better clinical outcomes, improved patient satisfaction and access to new therapies etc.) based on the attributes of specific product candidate cases. The aim is to provide the theoretical foundation for an economic evaluation of product candidates, as precursor to the development of models to forecast pricing and revenue scenarios (on a per-patient basis) in current and potential market channels.

Develop advanced system and organisational level models to describe and map the different operational business scenarios for creating and delivering value through implementation of centralised or RDM approaches that leverage cell micro-factory and 3D printing technologies. The aim is to provide a framework to support a quantitative and comparative evaluation (e.g. cost-benefit, cost-effectiveness and/or cost-utility analysis) of the economic value of the expected benefits to the hospital and the broader healthcare system that RDM confers, compared with conventional centralised product provision. This will provide the basis for impact-led case studies with market access stakeholders.

Develop and configure advanced system and organisational level models to map a range of operational business convergence scenarios for adoption of 3D-printing as a complementary manufacturing system for the pharmaceutical industry. The aim is to provide the basis for impact-led collaborative case studies to test such hybrid systems for specific niche applications and analyse opportunities for extending value in existing, conventional pharmaceutical pipelines and supply chains. This may cover the customisation of existing solid dosage forms and reduction of material wastage.

O2 Establishing customer interfaces and pathways for adoption

Establish a multi-perspective working group (industry, NICE, NHS, government representatives) to consider the healthcare market challenges to adoption of manufacturing technologies and commercial operations in hospital settings to gauge the impact of external supply-side factors, external demand-side factors and internal health service factors on adoption decisions. The aim is to provide a framework to develop realistic decision tools to support and incentivise technology adoption. This is a prerequisite for identifying optimal pathways for adoption and for development of models to forecast market uptake/penetration rates that are needed to optimise capital expenditure and incentivise investment in technology development.

Establish a working group (industry, NICE, NHS, government representatives) to review and investigate opportunities to exploit existing and emerging initiatives, including the Accelerated Access Review (AAR), NICE modelling and NHS specialised commissioning programmes, as potential pathways for adoption and market access.

Investigate potential future opportunities to exploit the Accelerated Access Pathway proposed by the AAR for early implementation of selected RDM advanced therapy focused pilots.

Establish working group to define the products, services, partnership arrangements and supporting infrastructure (Product Service System) required to implement and deliver the level and extent of servitisation required to navigate the customer-centric solution space (e.g. the user driven, customised or personalised product design space). The aim is to develop and test new manufacturing organisational models that provide optimal benefits for the innovator company and for the customer.

Establish a working group to consider the challenges to forming the collaborative partnerships with the NHS that will be required to build capacity for RDM. This should examine reconfiguration of supply chains and logistics, viability of business models, and the role of hospitals to support the commercial manufacture and formulation of advanced therapies. The aim is to support ongoing discussions to establish a network of Cell and Gene Therapy Treatment Centres.

Develop an organisational framework to broadly categorise and describe the type and location of interactions between the customer (as the manufacturer) and the central supplier (machine producer and/or franchise). The aim is to provide the basis for mapping the customer-touch points in each selected market channel. This serves as a precursor for identifying potential barriers to servitisation and opportunities for aligning internal processes and capabilities to enhance customer relationships for different operational business scenarios for RDM.

Cross-industry regulatory case studies to examine the status of adoption of 3D-printing (e.g. in automotive, aerospace, defence industries as early adopters) to identify and address potential barriers to the adoption of 3D-printing technology as a complementary manufacturing system in the pharmaceutical sector.

O3 Reconfiguring the organisational value system

Engage with stakeholders from regional healthcare trusts to further explore opportunities to develop and implement a pilot regional Hub for the provision of aseptic goods manufacturing and supply services. The aim is to build on the concept of a 'Collaborative Enterprise Network' that has previously been developed and trialled with Midlands NHS Trust stakeholders, as a basis for forming a network of similar hubs in other parts of the UK.

Engage with stakeholders to implement in-depth mapping and analysis of existing healthcare delivery configurations and NHS supply networks (*including national/regional cell and tissue transplantation supply chains, national blood supply chains, hospital pharmacy networks, prosthetic networks and national networks for personalised medicine*). The aim is to identify and stratify current physical and digital infrastructure capacity/capability constraints and human resource capability gaps that underpin the main processes linked to a foundational state of institutional readiness.

Draw on outcomes from NHS supply network gap analysis to establish the core capability and infrastructure requirements (at facility and network levels) and provide a basis for evaluating the scale, scope and cost of raising the level of institutional readiness for deployment (installation, set-up and operation) of supplied commercial cell micro-factory or 3D-printing production systems in hospital settings.

Establish a working group to extend the analysis of supply models to identify and assess the regulatory/legal risks related to infrastructure and product/service lifecycle management and governance. This provides a risk-based framework for developing models of servitisation and for implementation of information system solutions, with the aim of mitigating exposure to regulatory risk and administrative burden across sites and optimising the degree of autonomy of each hospital site in the network.

Supported by cross-industry case studies (e.g. aerospace, defence industries), explore the information technology and Industry 4.0 landscape to determine the core enablers for establishing the interconnectivity between discrete aspects of the RDM supply chain models and the industrial operational environment. The aim is to identify where the principles can be applied to the deployment of the production technology and the organisation of the service-orientated infrastructure.

Establish a cross-functional working group (customers and technology partners) to create an initial pilot project to establish proof of concept, targeting the transfer of a selected manufacturing technology prototype (e.g. 3D-printer) into one or two hospital sites and market channels. The aim is to gain real-world insights into the vertical and horizontal operational processes and functional workflows that need to be implemented and integrated to enable routine commercial manufacturing in a hospital setting.

Establish an industry group to design and develop new manufacturing skills packages and delivery mechanisms to grow a technician and operator workforce capable of reliably running routine manufacturing operations. The aim is to deliver responsive programmes across future sector-specific RDM-enabling production platforms, leveraging existing or proposed broader skills development initiatives.

Establish an industry group, supported by appropriate NHS stakeholders, to develop responsive programmes to address relevant future, sector-specific product technology skills and knowledge gaps of current and future clinical professionals. The aim is to align and leverage existing strategies and training programmes to advance the R&D knowledge and skills base among the NHS workforce (e.g. NIHR research training programmes for clinical professionals and NHSE personalised medicine strategy). This underpins the need to encourage greater involvement of the next generation of clinical professionals, pharmacists, prosthetists and surgeons in commercial R&D functions for emerging regenerative medicine therapies and 3D-printed medicines.

O4 Designing commercially viable financial structures

Establish a pre-competitive working group to develop new cost modelling methodologies to categorise and quantify the cost elements for implementing and operating centralised and redistributed manufacturing and supply approaches that leverage cell micro-factory production platform technologies for the manufacture and delivery of autologous and/or allogeneic CATBTs. In the context of hypothetical case examples, the aim is to provide the basis for a comparative analysis of cost structures, in terms of accurately quantifying the proportion of fixed and variable costs to total costs and the factors that influence the final pricing strategy. The outcomes will provide a consensus view on which redistributed operational business scenarios can confer commercially viable economies of scale and scope for maximising revenue and in so doing create the confidence that underpins the required investment in the development of RDM strategies for CATBTs.

Develop new methodologies to build an experimental data-driven framework to categorise and quantify the cost elements for implementing and operating centralised and redistributed manufacturing and supply approaches that leverage 3D-printing technologies. In the context of hypothetical case examples, the aim is to provide the experimental basis for the development of cost structures that accommodate hidden costs related to ancillary manual processes and to the risk of build failure or part rejection.

Extend models for forecasting market uptake/penetration to establish the projected manufacturing capacity required to support access to current and potential UK markets. The aim is to provide the experimental basis for establishing the optimal economy of scale and rate of capital expenditure to mitigate investment risk in capital equipment acquisition and/or facility build.

O5 Establishing viable routes to EU market access

Establish a market access stakeholder working group to consider how the unique clinical and economic performance attributes of the redistributed product-service dimension of therapeutic models may challenge conventional healthcare valuation and reimbursement decision frameworks; for instance, by conferring proportionate benefits to both the patient and the healthcare system aggregated across distributed sites. The aim is to provide the basis for establishing a common language and evaluation criteria to aid understanding of the ways RDM represents value for money and for identifying stakeholder concerns/barriers to uptake of RDM approaches across the healthcare system.

Drawing on a review of existing initiatives in the field of advanced therapies, hypothetical case scenarios should be extended to investigate alternative payment and financing models that can be tailored to the specific attributes of the product groups targeted for RDM in hospital settings or other market channels. As a prerequisite to engaging market access stakeholders, the aim is to provide a decision framework to explore and develop models that are implementable in short/mid-term timeframes. This must adequately consider value relative clinical and economic benefits, management of shared risk between multiple stakeholders, the need to minimise patient/caregiver economic burden and up-front cost, and patient access affordability. Outputs should provide the precursor to the development of proposals/recommendations as a basis for discussion with market access stakeholders to further define and prioritise the necessary steps to address legislative and logistical barriers to implementation.

Establish product data interoperability group to develop digital platforms for standardising the collection of product performance data (i.e. clinical trial, product release and post-marketing data) in aggregate and for individual patients. The aim is to build a real-time, visible therapeutic network to accelerate clinical experience that (with appropriate permissions and data safeguards) could be shared with public and private payers in performance-based arrangements and coordinate pull-through and market access across distributed sites.

Establish a product data interoperability group to develop digital platforms for standardising the collection of patient-specific 3D-printed drug performance data. The aim is to build a real-time, visible database for individual patients to enable patient-specific formulations and dosages to be adjusted according to phenotypic evidence of intended results and undesirable side effects.

APPENDIX C – ACKNOWLEDGEMENTS

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) for funding the Redistributed Manufacturing in Healthcare Network (RiHN), grant reference EP/M017559/1.

The RiHN Programme and its funded feasibility studies also conducted notable research engagements and events with a number of external organisations and networks, who contributed valuable expertise, support and access to resources. We extend our thanks to the following:

- 3DP-RDM: Defining the research agenda for 3D printing enabled redistributed manufacturing
- Association of the British Pharmaceutical Industry (ABPI)
- Building sustainable local nexuses of food, energy and water: from smart engineering to shared prosperity (The Local Nexus Network)
- Cell & Gene Therapy Catapult
- CellData Services
- CMAC Future Manufacturing Research Hub
- Defence Medical Services, Ministry of Defence
- European Medicines Agency (EMA)
- FujiFilm Diosynth Biotechnologies
- GlaxoSmithKline (Cell & Gene Therapy Platform)
- Laborie-MMS
- Medical Research Council (MRC)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Medicines Manufacturing Industry Partnership (MMIP)
- Medilink East Midlands
- NHS Pharmacy, Leicester Hospitals
- NHS Regional Medical Physics Department, Freeman Hospital Unit
- Pfizer
- RECODE Consumer Goods, Big Data and Redistributed Manufacturing
- Re-Distributed Manufacturing Networks – The Role of Makespaces
- Redistributed Manufacturing and the Resilient, Sustainable City (ReDReSC)
- REMEDIES (RE-configuring MEDIcines End-to-end Supply) Project
- Royal Centre for Defence Medicine (RCDM), University Hospitals Birmingham
- School of Life and Health Sciences, Aston University
- VoiceNorth
- West Sussex County Council

Cell and Tissue-based Therapeutics (CATBTs)	Cell Factory
Tissue engineered ATMPs	3D-Printing
Diagnostic Medical Devices	
Solid Dosage Forms	
Product Candidates	**Core Technology**

APPENDIX D

RESEARCH CHART: LINKING NEEDS, CHALLENGES & FUTURE PRIORITIES FOR R&D

This diagram illustrates the systematic linkages between the 'needs' driving RDM, 'challenges' (Appendix A) that need to be overcome and 'priority areas' for future R&D (Appendix B); covering cell microfactories and 3D-printing.

Codes with A1, A1-2, A2, A3, A4 correspond with Appendix A1, A1-2, A2, A3, A4
Codes with I1, I2, I3 correspond to Appendix B1
Codes with I4, I5, I6, I7, I8 correspond to Appendix B2
Codes with R1, R2, R3 correspond to Appendix B3
Codes with O1, O2, O3, O4, O5 correspond to Appendix B4

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