Point-of-care manufacture of advanced therapies: readiness measures for hospitals, companies, and regulatory agencies

Advanced Therapy Medicinal Products (ATMPs), such as cell and gene therapies, are promising for treating rare diseases, as well as some more prevalent conditions such as severe burns or diabetes. In some cases, it is necessary to adopt models where ATMPs are produced in clinical settings and immediately delivered to patients (point -of-care manufacture). This could enlarge the range of innovative therapies made available in the NHS, but also brings about considerable challenges.

Introduction

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has proposed a new regulatory framework dedicated to the production of therapies in hospitals.[1] This framework aims to provide more flexibility to the production of medicines, including ATMPs. Whilst this flexibility might encourage innovation and development of new ATMPs, a regulatory framework alone is not sufficient to enable medicines to be manufactured on demand, closer to the patient. This vision will be more thoroughly realised if various stakeholders seek coordinated ways of working, which will require some adjustments to their current operations. This document highlights some readiness measures that can be taken by three groups of stakeholders – healthcare system and hospital staff (including NHS Trusts, clinical centres, commissioning groups), companies, and regulatory agencies – thus complementing the MHRA's initiative. Drawing on an academic research project being conducted at University College London,[2] we aim to contribute towards the successful implementation of point-of-care manufacture at larger scale.

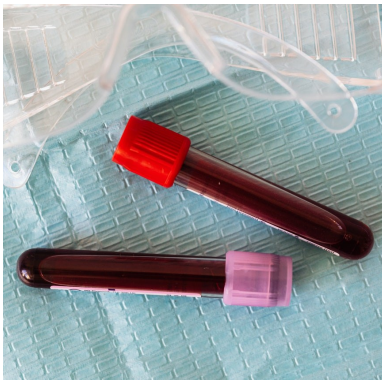
Key recommendations

To implement point-of-care manufacture at larger scale, some readiness measures would be beneficial for the following groups:

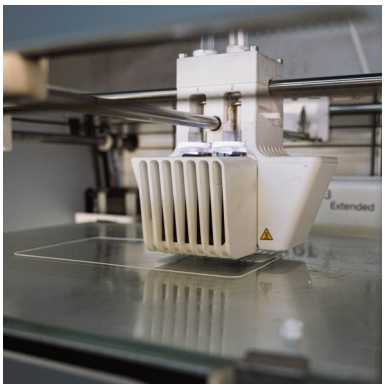
1. **Hospitals** would benefit from training staff (including professionals who may act as assistants to Qualified Persons), adjusting infrastructure (including storage space and stem cell laboratories), reviewing the standards generally used by the industry, and updating governance frameworks.
2. **Companies** would benefit from enhancing transportation systems for biological materials and reagents, developing data management systems for use in hospitals, and engaging in dialogue with regulators to establish processes for therapy release.
3. **Regulators** would benefit from strengthening horizon scanning activities and seeking proportionate regulatory assessments for manufacturing systems that will be highly flexible.

Which products are most likely to be manufactured at the point-of-care?

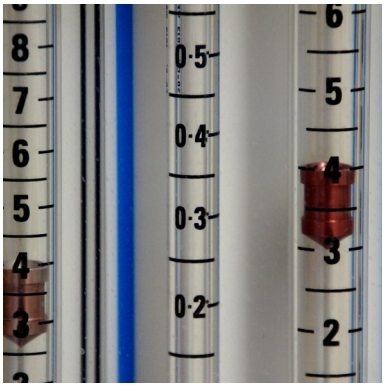
1. ATMPs: medicines derived from gene editing, cell manipulation or tissue engineering



2. Blood products: therapies prepared from human blood



3. 3D-printed products: products derived from additive manufacture



4. Medical gases: used for treatment and anaesthesia

What are ATMPs?

According to the European Medicines Agency (EMA), Advanced Therapy Medicinal Products (ATMPs) are any of the following products: a gene therapy medicinal product; a cell therapy medicinal product; a tissue-engineered product; or one of the products above combined with a medical device. Currently, their development and use are regulated by the ATMP Regulation of the European Union (Regulation No 1394/2007), which came into force in 2008.

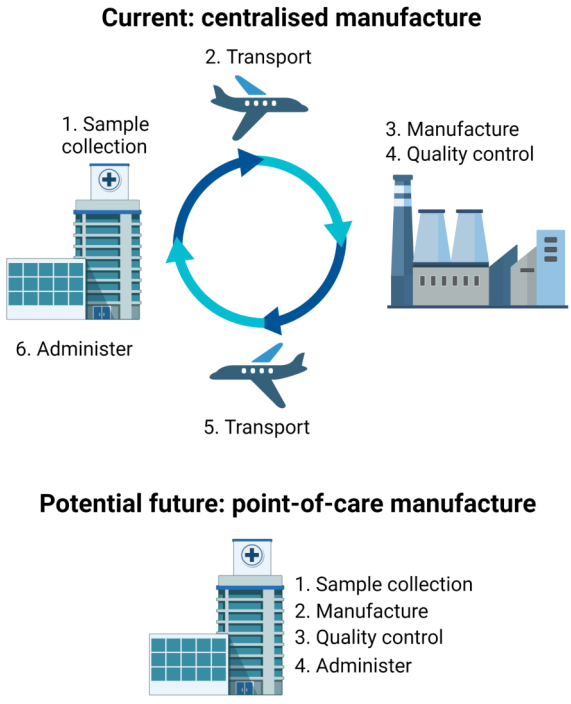
According to the ATMP Regulation, these products must be manufactured in line with Good Manufacturing Practices (GMPs), meaning that their production must follow a series of procedures to ensure high quality. As a result, ATMP manufacture brings about particular challenges[3], requiring sophisticated infrastructure and equipment, as well as skilled personnel.

Some ATMPs are designed based on the clinical or even genetic features of each patient (making them genuinely personalised medicines). These personalised ATMPs are particularly promising for illnesses for which no treatment has been found. For example, they have been the only route available to clinicians in some resistant cancers and some serious eye conditions, with potentially life-changing outcomes. At the same time, several scientific and technical challenges must be overcome for these therapies to become more effective and widespread, such as gaining better knowledge of different cell types.

Why manufacture ATMPs at point-of-care?

Currently, ATMPs are manufactured in a few centralised sites, with starting materials and/or final products being generally frozen for transportation. For some ATMPs currently under study and development, freezing and transportation may reduce the

Figure 1. *Centralised vs. point of care manufacturing*



therapy's potency. Thus, the therapy has to be delivered to the patient some minutes or even seconds after its manufacture has been completed.

For example, Biotherapy Services, a company based in England, has manufactured a blood product for chronic wounds at point of care. As manufacture is completed, the product begins to degenerate, having therefore to be immediately delivered to the patient. Currently, the company operates in seven clinical sites but wishes to increase this number to thirty sites in the next three years, (Figure 2).

Biotherapy Services offers a blood product, not an ATMP, but its manufacturing solution can be replicated, with some adjustments, by manufacturers of ATMPs which will also have a short shelf life. Therefore, even though the implementation of point-of-care manufacture brings about several challenges that are yet to be overcome,[2,3] it is possible to envisage a future where manufacturing activities will be carried out in hospitals whenever a certain type of therapy is needed.

Point-of-care manufacture can then put hospitals in contact with cutting-edge products, refining the therapeutic skills that they hold, and increasing the range of therapies made available to patients. It also makes it possible to operationalise manufacturing activities as a service commissioned by the health system, enabling a market exploration that is in line with the rationale of the life sciences policies adopted in the UK over the last decade.[5,6]

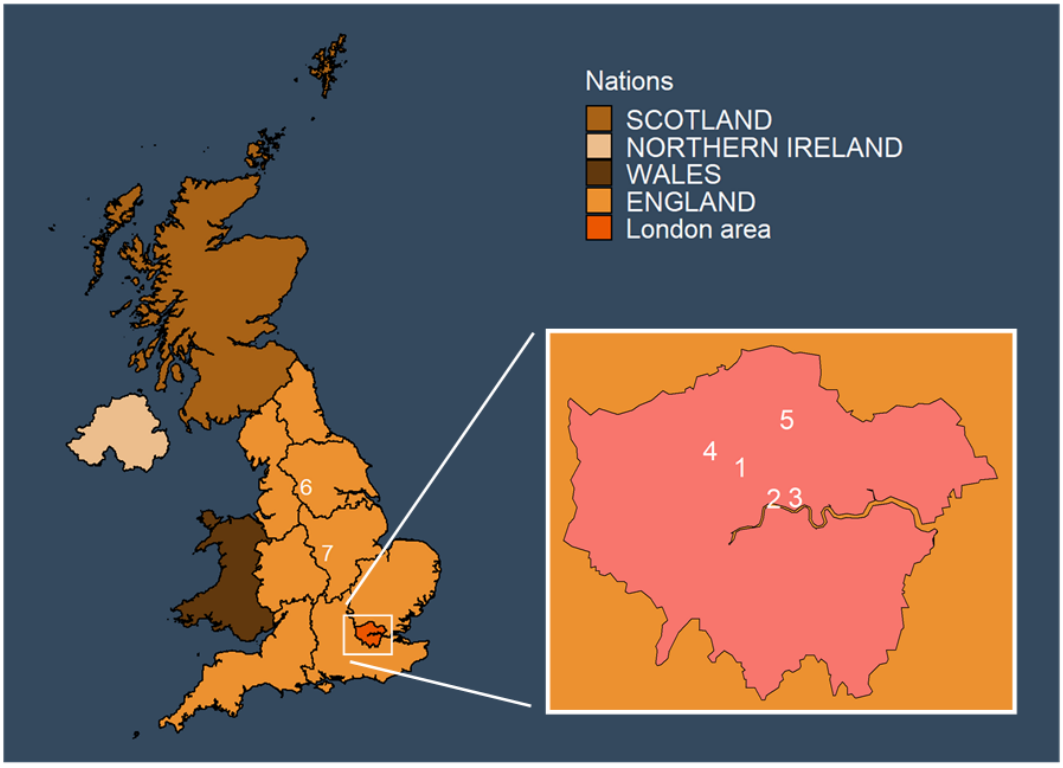
How does the MHRA intend to regulate point-of-care manufacture of medicinal products?

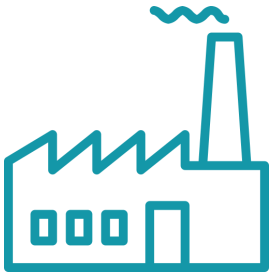
In the UK, the MHRA is responsible for ensuring quality and safety in the development and delivery of medicines and medical

"This is a clear example of proactive and responsive regulatory action, where the MHRA identified a step-change in approach to medicines development and manufacture that will benefit from and require changes to the regulatory framework"

- Ian Rees, the regulatory science expert who is leading on the work for the MHRA[17]

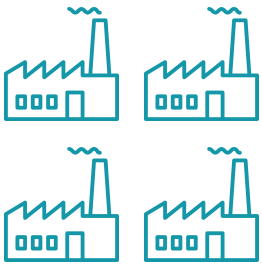
Figure 2. *Manufacturing sites of Biotherapy Services: March 2022.[4]*





3 to 5

The average number of manufacturing facilities for conventional medicines[4]



200

The projected number of hospitals where a product now in clinical trials will be manufactured (according to the MHRA).

devices. The agency has noted the scientific and technical trends which increase the viability and necessity of therapy production in hospitals. As a result, they have proposed a regulatory framework specifically dedicated to governing the processes of point-of-care manufacture.

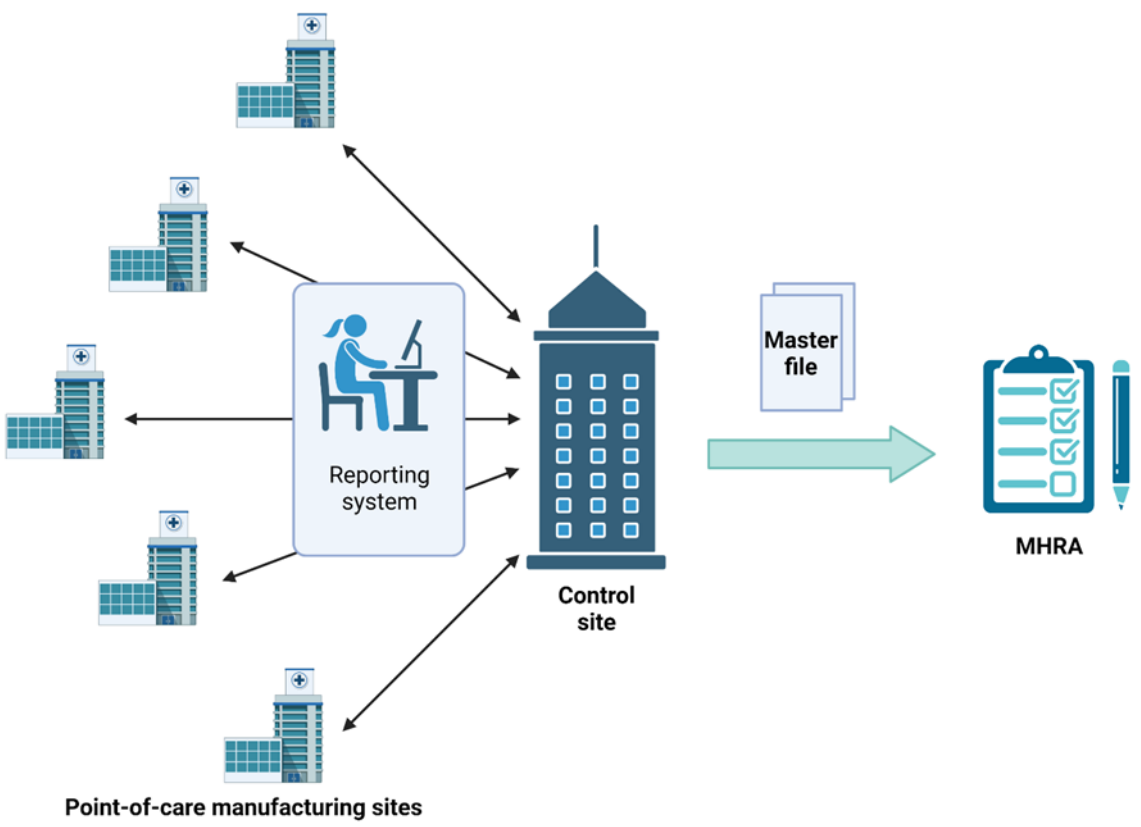
The proposal covers a broad range of therapies, including ATMPs. It was subject to public consultation in 2021[1] and is expected to go through legislative process and be approved into law in 2022.

Since decentralising therapy manufacture will increase the number of manufacturing sites, it might be more challenging for the MHRA to carry out its inspecting duties. As a solution, the MHRA has proposed the concept of "Control Site": the institution or company that will be responsible for the manufacturing system, selecting and inspecting hospitals where manufacture will occur, providing equipment and training to those hospitals, and collecting relevant information about manufacturing processes. The product is expected to move through all phases of clinical development, including clinical trials and marketing authorisation.

A reporting system will ensure constant (and, if necessary, real-time) communication between the Control Site and the manufacturing sites. Information on the activities of manufacturing sites will be recorded in a "Master File" and submitted by the Control Site to the MHRA, (Figure 3).

In order to realise the vision set out by the regulatory proposal, different stakeholders can take a number of important steps to be ready for ATMP point-of-care manufacture. In the next section we will look at some initiatives that can be adopted by three groups of stakeholders – healthcare system and hospital staff, companies,

Figure 3. *The MHRA's regulatory framework proposal*



and regulators – to make sure that GMPs are followed in point-of-care manufacture, thus delivering safe and effective medicines to patients. The aim is not to propose an exhaustive list, but to introduce measures that can, in the short term, enhance the UK's preparedness for point-of-care manufacture.

How can Trusts, clinical centres, and hospitals ready themselves?

Depending on scientific and technical advances, point-of-care manufacture may become less complex and more viable for hospitals in the coming years. As this trend is consolidated, hospital staff may need to change some of their current procedures in order to accommodate manufacturing activities in the clinical setting.

Clinical staff and hospital administrators can promote some institutional changes to ready themselves for ATMP point-of-care manufacture:

- Be aware of the Advanced Therapies NHS Readiness Toolkit, which has been prepared by the Advanced Therapies Treatment centres and involves several aspects of ATMP processing in hospitals.[7]
- Develop or extend terms of reference for ATMP committees (which have been established in some hospitals to oversee research and clinical activities involving advanced therapies) so these committees' activities cover point-of-care manufacture, as well as define the roles that should be represented in those committees.
- Train staff in order to have at least one member of staff who could, for example, act as a "nominated individual"[1] by liaising with the Qualified Person[8] (responsible for assuring the quality of medicines) based in the Control Site. Technical service pharmacists may be suitable to play this role given their understanding of pharmaceutical quality systems.
- Review the Governance Guidelines, Standard Operating Procedures, and Pharmacy Institutional Readiness Guidance being designed by the Pan-UK ATMP Pharmacy Working Group, assessing the viability of their implementation.[9]
- Seek dialogue with Trusts where ATMPs are already being deployed (the Pan-UK Group constitutes a suitable environment in this regard).
- Review the requirements mandated by the Human Tissue Authority for working on biological materials,[10] as these requirements may apply, for example, when starting materials are collected and/or stored by the hospital's clinical staff.
- Consider how point-of-care manufacture might affect future requirements for infrastructure (including stem cell laboratories, pharmacy facilities, leukapheresis devices, and cryopreservation facilities), and ensure that these are factored into infrastructure planning and upgrades.
- Commissioning players (such as NHS England and Clinical Commissioning Groups) would also benefit from evaluating whether and how the gradual adoption of technical standards

For ATMPs manufacture, Good Manufacturing Practices (GMPs) must be followed to ensure quality and safety.

Important information on point-of-care manufacture will be stored in a Master File shared with the MHRA

Master File systems have been used in the fields of Plasma and Vaccine Antigens.

1 year

the shelf life of Yescarta, an ATMP centrally manufactured by Gilead Sciences, for the treatment of two types of lymphoma.[16]

15 seconds

The time allowed between completion of manufacture and delivery to patient for a blood product manufactured at bedside by Biotherapy Services, a UK company.

related to manufacturing activities impacts on the clinical and data processing activities carried out in hospitals.

- NHS can seek strategies for developing standardised data processing and reporting systems, which could be rolled out across the healthcare system. Equally, it would be important to promote investments in disease registries and referral pathways, so that patients who may benefit from ATMPs can be identified and treated.
- Trusts and clinical centres can also conduct surveys or studies to understand the availability and preparedness of clinical staff to potentially take on additional manufacturing and oversight responsibilities.

How can companies developing ATMPs ready themselves?

The prospect of point-of-care manufacture opens up business models for ATMP developers such as pharma and biotech companies, but at the same time creates new layers of complexity, which may be overwhelming, especially for spin-outs and middle-sized companies. There are some preparatory measures that these companies can adopt:

- Reinforce strategies for designing the clinical implementation process concurrently with the product.
- Initiate an early dialogue with the MHRA, which provides guidance and specialised support to companies.[11]
- Engage in a dialogue with stakeholders exploring manufacturing equipment and solutions, which may involve companies producing manufacturing platforms, as well as institutions such as Cell and Gene Therapy Catapult.[12]
- Partner with academic groups specialising in the development of bioengineering and data analysis solutions for personalised medicines, such as UCL Future Targeted Healthcare Manufacturing Hub.[13]

How can other relevant companies ready themselves?

Point-of-care manufacture will indirectly involve other kinds of companies, for example those responsible for transporting materials or developing data management systems. Readiness measures can also be adopted by these companies:

- Point-of-care manufacture can involve relatively complex supply chains, and some consumables and reagents may be directly delivered to hospitals. In this case, transportation companies and medical couriers can review standards that have been increasingly required in the NHS, especially ISO 9001, ISO 14001, and ISO 27001.
- Point-of-care manufacture can imply the use of some equipment, either in the form of specialised manufacturing equipment (such as platforms for automated cell processing) or in the form of auxiliary devices (such as shakers, incubators or bioprinters). Companies manufacturing this equipment can investigate how it can be used in clinical settings where the availability of space and highly skilled operating personnel may be limited. Collaboration with the MHRA and NHS Trusts will also be necessary to find suitable maintenance schemes,

considering that technical expertise for maintenance may be limited in hospitals and in some Control Sites.

- Companies offering IT and software packages and solutions to hospitals can investigate how their products could fulfil the needs of clinical staff. They should look at this challenge in light of cybersecurity and data protection requirements (such as the ones embedded in the UK Data Protection Act[14]), as hospitals deal with sensitive patient information.

How can regulators & health technology assessment agencies ready themselves?

The MHRA's regulatory framework proposal on point-of-care manufacture has implications not only for the MHRA itself but also for other agencies directly or indirectly responsible for activities carried out in hospitals. Since a new regulatory rationale is being introduced, it should be scrutinised and, if necessary, assimilated by other regulators by means of the following initiatives:

- The MHRA can reinforce its dialogue with the Health Research Authority, working towards the design of a combined review process that could cover both the Clinical Trials Authorisation and the research ethics approval, bearing in mind that some products may be manufactured in large numbers of hospitals.
- The MHRA can encourage the adoption, across the point-of-care manufacture landscape, of unified inspection standards and quality management systems, which would prevent a multiplication of procedures and systems to be deployed in hospitals.
- For agencies overseeing research, such as the Health Research Authority, it is important to investigate the ethical effects of a new type of clinical study where therapy manufacture no longer happens in a specialised manufacturing facility, and begins to happen in the hospitals' premises, near the patient.
- For agencies responsible for specific regulations and guidance, such as the Human Tissue Authority or the Health and Safety Executive, it is important to enhance horizon scanning activities

The Future Targeted Healthcare Manufacturing Hub

The current "one-size-fits-all" approach to drug development is being challenged by the growing ability to create stratified and personalised biological medicines for groups of patients and even individuals. Many of the approaches in this new class of medicines use advances in gene editing technology and have the potential to cure, and not just treat, patients.

The FTHM Hub is addressing manufacturing, business and regulatory challenges to ensure that new targeted biological medicines can be developed quickly and manufactured cost-effectively.

To find out more about the FTHMH, please visit: www.ucl.ac.uk/biochemeng/hub

Figure 4. Critical steps in point-of-care manufacture and control measures

Immediate control	Testing starting materials.	Testing patient samples.	Assurance of manufacturing process.	Testing a sample of the product (if possible).	Monitoring and management of possible adverse reactions.
Critical activities	Reception of starting materials 	Collection of patient samples 	Manufacture 	Final product 	Patient reaction 
Long-term control	Certification and inspection of suppliers of starting materials.	Constant monitoring of collection procedures.	Certification and maintenance of equipment. Training of staff.	Constant refinement of critical quality attributes.	Constant improvement of therapies. Constant update of clinical protocols.

References

1. MHRA. Consultation on point of care manufacturing. 2021.
2. Bicudo, E.; Brass, I.; Carmichael, P.; Farid, S. 2021. The UK's emerging regulatory framework for point-of-care manufacture: insights from a workshop on advanced therapies. Cell & Gene Therapy Insights, 7(9): 1005-1015.
3. Rafiq, Q. A.; Harrison, R. P. 2019. Supply chain considerations and strategies for regenerative medicine products. Reference Module in Biomedical Sciences: 71-80.
4. MHRA. March 2022. Human and veterinary medicines: register of licensed manufacturing sites.
5. Life Sciences Industrial Strategy. Especially p44 and 46.
6. Association of the British Pharmaceutical Industry / UK BioIndustry Association / Innovate UK. Advanced Therapies Manufacturing Action Plan. 2016.
7. Advanced Therapy Treatment Centres. Advanced Therapies NHS Readiness Toolkit.
8. Royal Pharmaceutical Society. Qualified Persons.
9. Pan UK ATMP Pharmacy Working Group.
10. Human Tissue Authority. Licences, roles and fees. 2022.
11. MHRA. Scientific Advice.
12. Cell and Gene Therapy Catapult.
13. Future Targeted Healthcare Manufacturing Hub.
14. The Data Protection Act. 2018.
15. Regenerative Medicine Expert Group.
16. Electronic Medicines Compendium: Yescarta.
17. MHRA Horizon Scanning Case Study Point of Care Manufacture.

to anticipate significant issues associated with manufacture of products at point of care as they become more pressing.

- As ATMPs may contain genetically modified organisms (GMOs), agencies such as the Health and Safety Executive can assess the viability of developing a centralised GMO procedure. Currently, GMO approvals are not standardised nationally and are organised on a site-by-site basis, which can slow down the deployment of some ATMPs in hospitals.
- For the National Institute for Health and Care Excellence (NICE), it is important to anticipate updates in guidelines for therapies whose manufacture may happen in hospitals. It is equally key to evaluate how health technology assessments need to be adjusted when therapy manufacture ceases to be carried out in a company's facility and begins to rely on the infrastructure (and perhaps also some staff) of hospitals.
- For all agencies, it is important to reinvigorate the multi-institutional debate that takes place via initiatives such as the Regenerative Medicine Expert Group[15] where relevant issues pertaining to ATMP point-of-care manufacture could be identified and discussed.
- For all agencies, it is also important to consider that some ATMPs are personalised and there may be variance, for example, in the duration of the manufacturing process or speed with which relevant data on clinical responses can be collected. As a result, new regulatory frameworks will need to be flexible and proportionate, as the MHRA has demonstrated in its proposal.

Conclusions

Point-of-care manufacture of medicines is likely to become more frequent in the coming years. A series of readiness measures will need to be adopted by the different stakeholders involved. As these changes may have a considerable impact on hospital procedures, business models, and the work undertaken in regulatory agencies, it is key that all players become ready for new ways of working, which will make it possible to deliver cutting-edge therapies to patients in need.

Our research

This report was produced in partnership with UCL STEaPP's Policy Impact Unit (PIU) as part of the work carried out by the Regulatory Strategies team of the Future Targeted Healthcare Manufacturing Hub (FTHMH) comprising Dr Edison Bicudo (e.bicudo@ucl.ac.uk) - Research Fellow in Biopharmaceutical Regulation, Dr Irina Brass (i.brass@ucl.ac.uk) - Associate Professor in Regulation, Innovation and Public Policy, and Dr Penny Carmichael (p.carmichael@ucl.ac.uk) - Policy Engagement Specialist in the PIU. The findings and recommendations derive from: the professional and academic experience of the authors and contributors involved, and research findings from the FTHMH. This study has relied on a literature review, data collection, and qualitative interviews with professionals developing ATMPs.

Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) for the FTHMH hosted at University College London with UK university partners is gratefully acknowledged (Grant Reference: EP/P006485/1). Financial and in-kind support from the consortium of industrial users and sector organisations is also acknowledged.

Please cite this report as

Bicudo, E., Brass, I. and Carmichael, P. (2022) Point-of-care manufacture of advanced therapies: readiness measures for hospitals, companies, and regulatory agencies. Future Targeted Healthcare Manufacturing Hub, UCL.

Contributors

Dr Nicholas Medcalf - Visiting Professor in Regenerative Medicine Manufacture, Loughborough University. Anne Black - Regional QA Specialist Pharmacist and Qualified Person, NHS. Ryan McCoy - Senior Regulatory Affairs Manager, Cell and Gene Therapy Catapult

We would like to thank our contributors, who provided invaluable expertise, guidance, and input at various stages of this project. The report does not represent their views and any errors or omissions remain those of the authors.