



Point-of-Care Manufacture: Regulatory Opportunities and Challenges for Advanced Biotherapeutics

On 29 June 2021, UCL's Future Targeted Healthcare Manufacturing Hub (FTHMH) held an online workshop to discuss the concepts and rationale of a new point-of-care (POC) manufacturing regulatory framework in development by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). The proposal, which seeks to address the unique challenges of manufacturing healthcare products at, (or close to), the POC, is anticipated for publication and public consultation in summer 2021.

The workshop convened 32 specialists in the field of biotherapeutics, manufacturing technologies, and regulation. Through a series of talks and roundtable discussions, participants explored challenges of applying the regulatory framework to cell and gene therapies (also known as Advanced Therapy Medicinal Products (ATMPs)) manufactured at POC. Keynote speeches were given by representatives of the MHRA, Lonza (a chemicals and biotechnology company), and the FTHMH. This report summarises the key topics and findings discussed during the workshop.

Context: manufacturing advanced biotherapeutics

Two important advances have marked the development of advanced biotherapeutics based on cell and gene therapies in recent years. On the one hand, personalised, and potentially curative, therapies using live engineered cells have become a reality, though they can have a short shelf life if delivered fresh. On the other hand, new technological platforms have brought about opportunities in terms of scaling manufacturing out (to multiple sites) and down (for patient-specific therapies).

These trends create opportunities to design new manufacturing models that enable more decentralised production from regional manufacture (in a few large sites) through to POC manufacture (production of therapies at the bedside). These changes to the manufacturing process from mainly centralised to increasingly decentralised models require new regulatory frameworks to ensure the continued safety, efficacy, and quality of medicinal products manufactured outside centralised facilities.

Workshop aim

To inform the MHRA's Point-of-Care (POC) Manufacture Regulatory Framework and highlight opportunities and challenges the proposal raises for patient-specific advanced therapy medicinal products, such as cell and gene therapies.

Key findings

1. **Quality control:** Analytical tools will be needed to support quality control across multiple sites and minimise reporting errors.
2. **Equipment and standardization:** Manufacturing systems and devices should be standardised between sites to avoid product variability.
3. **Human resources:** Effective and reproducible training schemes are needed to support manufacturing across multiple sites.
4. **Hospitals:** Relations between manufacturers and hospitals should be managed to ensure that POC manufacture is attractive, both technically and financially.

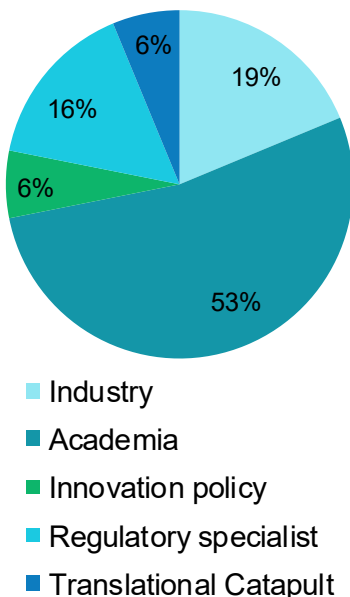
The Medicines and Healthcare products Regulatory Agency (MHRA)

The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices, and blood components for transfusion in the UK. The MHRA is an executive agency, sponsored by the Department of Health and Social Care.

The Future Targeted Healthcare Manufacturing Hub (FTHMH)

The FTHMH is addressing the manufacturing, business and regulatory challenges to ensure that new targeted biological medicines, including cell and gene therapies, and stratified proteins, can be developed quickly and manufactured cost-effectively. With over 40 partnering organisations, the Hub has huge convening power which it uses to drive forward the agenda for research and innovation in targeted biological medicines.

Workshop attendees by sector



1. As shared by the MHRA during the 29 June workshop

In the UK, the MHRA has identified this opportunity and the need to create dedicated regulation for POC manufacture. Between 2020-2021, the MHRA organised three workshops to obtain insights on POC manufacturing for a range of healthcare products from key stakeholders. These workshops were attended by members of the FTHMH. We set out our understanding of the MHRA’s proposal in the next section.

The MHRA’s POC Manufacture Regulatory Framework Proposal

The MHRA’s POC Manufacture regulatory proposal aims to develop proportionate regulation that:

- has control measures equivalent to those currently in place for traditional pharmaceuticals such that POC products have appropriate safety, quality, and efficacy properties;
- supports a broader range of manufacturing and supply options for patients to access new treatments; and
- accommodates future developments.¹

The regulatory framework covers a broad range of highly personalised products including blood products, gaseous products, ATMPs, and small molecule products that generally have a short shelf life (from only a few seconds to a few hours), necessitating manufacturing at POC.

From the regulator’s perspective, one of the main challenges of POC manufacture is quality control as an increasing number of POC products will be manufactured across a large number of sites. To address this issue, the regulatory proposal introduces the concept of a “Control Site” – a new entity responsible for establishing and overseeing the manufacturing process occurring at several manufacturing sites that fall under its remit.

All the information pertaining to the manufacture system will be stored in a POC Manufacture Master File. The content of this document, as well as the frequency of its update, may vary with the nature of the product. The Master File will always provide information on: GMP inspections; staff; adverse events; batches; patients receiving the product; and participating sites. In this manner, the regulatory proposal introduces a layered system where the Control Site figures as an entity mediating between the MHRA and the sites, as illustrated in Figure 1.

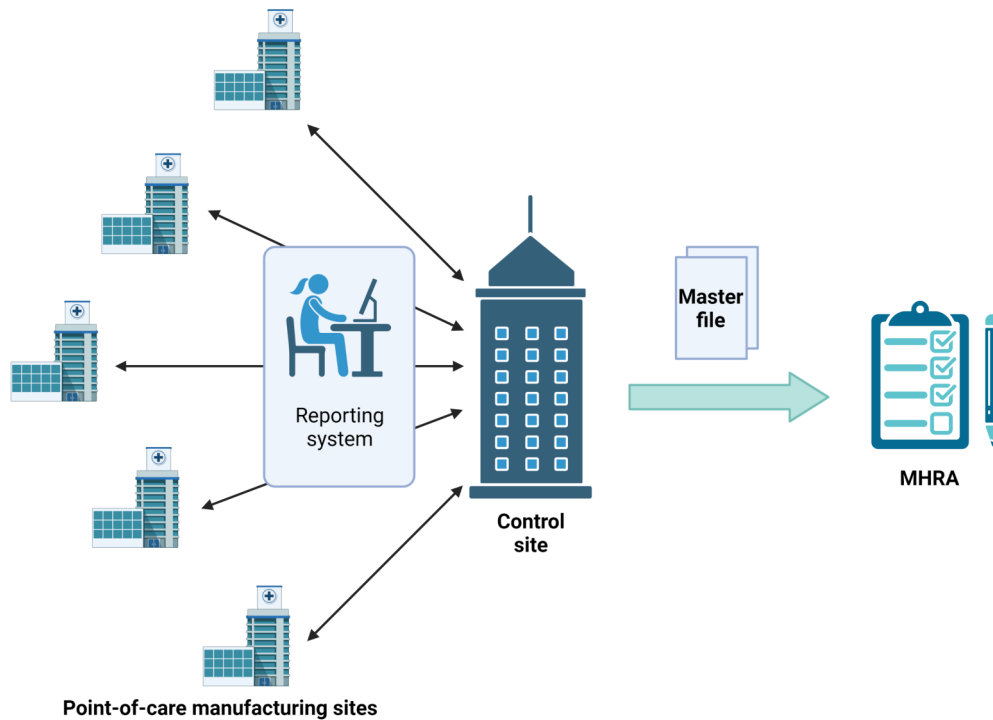
Summary of workshop discussions on the POC Manufacture Regulatory Framework proposal

Generally, the workshop participants had a positive view of the MHRA’s proposal but also pointed to some aspects that would benefit from further refinement and consideration. Four main themes were discussed: quality control, equipment and standardization, human resources and training, and implementation in hospital sites.

1. Quality control

When many sites are mobilised, it can be difficult to put in practice the concept of equivalent control measures. The main challenge is that small procedural changes may be implemented at each manufacturing site, either consciously or unconsciously. For example, software updates may be implemented at different times across different manufacturing sites, which may introduce minimal variations in systems that rely on software support for different tasks. Thus, it is important to minimize the chances of discrepancies between different sites. In this regard, data

Figure 1: A schematization of the MHRA's regulatory proposal. Created with BioRender.com



integrity, automated software updates, and continuous monitoring will be crucial.

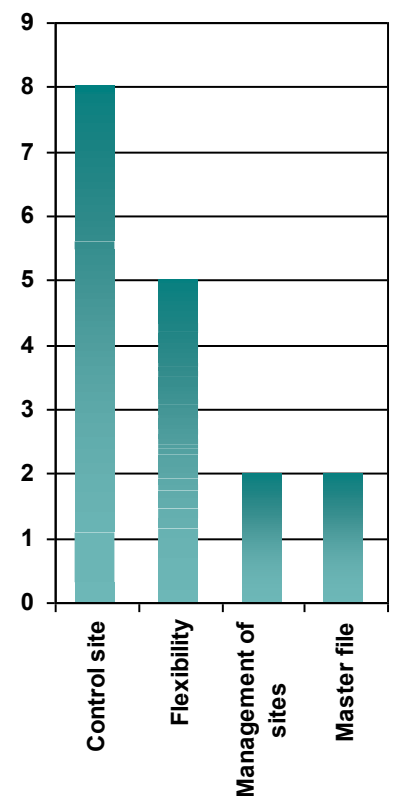
Pre-production checks of equipment and raw materials are a critical stage in Good Manufacturing Practice (GMP). This is exacerbated by the need to handle a broad range of incoming materials, making it difficult to decentralize all aspects of quality control. Thus, it is probable that some materials will be tested and approved centrally, being subsequently released for use in clinical settings.

In addition, some workshop participants expressed difficulty imagining a system that is so diverse (involving many POC manufacture sites) and widespread (covering a broad geographical area) being monitored by a single Control Site. MHRA representatives confirmed that the framework also covers off-site qualified person (QP) release, whereby the QP monitors the manufacturing process without having to be physically present at the site. However, this type of QP monitoring will only be viable with highly automated manufacturing systems and, ideally, real-time monitoring.

Lastly, accurate quality control will depend on the features of the Master File. Several workshop participants noted that it is important to have a clearer idea of the nature and organization of this document, as well as how the File's information can be used along the path leading to product registration and marketing authorisation.

2. Equipment and standardization

A major challenge in POC manufacture will be the variability between manufacturing sites, which can compromise product quality and generate new risks. This difficulty can be solved, or at least minimized, by means of closed, automated manufacturing systems. In this way, risk assessment and control requirements can be simplified, even though questions remain about the readiness of existing manufacturing platforms to be used in a POC setting. In addition, it is known that substantial investment may be required for data integrity systems to be put in place to enable such technical monitoring of site variability. In



During the workshop, we asked participants to tell us which aspect of the MHRA's regulatory proposal they considered as the strongest point. The results show that workshop participants identified the Control Site proposal and the flexible approach taken to apply the framework to a wide range of products and manufacturing processes as the strongest elements of the regulatory framework.

Workshop speakers



Ian Rees, Unit Manager Inspectorate Strategy and Innovation, MHRA, who introduced the rationale and main concepts of the MHRA's POC regulatory proposal



Laura Sands, Head of Regulatory Affairs, Personalized Medicine, Lonza, who spoke about the technical features and opportunities of the company's Cocoon cell therapy manufacturing platform



Dr Qasim Rafiq, FTHMH Co-Investigator in ATMP Manufacturing, who spoke about the main technology barriers and drivers for manufacturing cell and gene therapies at the POC

some cases, this may prove financially infeasible, especially as the number of sites and patient populations grow.

3. Human resources

Since trained staff must be present to perform tasks such as pre-process checks and manufacturing device operation, ensuring sufficient provision of training for POC personnel emerges as a major challenge. If hospital staff are to participate in manufacturing activities, then those individuals will need to undergo training in ways which are not yet clear. Standardized training procedures can be proposed, but it is not always simple to put them in practice. Furthermore, clinicians may have little incentive to participate in such training, especially if the product is not manufactured very frequently. Therefore, the issues of mobilisation of staff, training, and workforce maintenance become pressing questions, as they can have decisive impacts on the final product's quality.

4. Hospitals

For hospitals, it may be too challenging to operate at GMP levels and comply with industry standards. They may struggle to deal with large supply chains and handle complex materials. Additionally, POC manufacture may not be attractive to hospital managers unless large patient numbers are involved.

The financial aspect of POC manufacture should also be taken into account. It is not clear whether hospitals will charge the sponsor company (or drug developer) for manufacturing activities happening on their premises or whether they will get a share of the therapy's reimbursement. For companies, manufacturing schemes can prove less attractive if the hospital receives a significant portion of the reimbursement.

Finally, an issue that needs clarification is the distribution of liability between POC manufacturing sites and the Control Site. As noted above, there may be deviations from the original manufacturing protocol. It is then important to know who is technically and legally responsible in manufacturing processes and systems that can reach high degrees of complexity.

Next steps

The MHRA are anticipated to launch public consultation on the regulatory proposal in summer 2021. The FTHMH will submit a response to this and continue to input to the development of the proposal where appropriate. In an upcoming academic publication, we will further explore this regulatory process development, as well as its possible implications for advanced biotherapeutics and similar POC products.

Our research

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

Contributors

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