CELL & GENE THERAPY INSIGHTS

DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

EXPERT INSIGHT

Point of care manufacture of ATMPs in the UK

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New legislation in the UK provides a flexible framework for the manufacture of cell and gene therapies at a patient's bedside.

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INTRODUCTION

The development and use of cell and gene therapies, including advanced therapy medicinal products (ATMPs), is accelerating in the UK, providing crucial treatment options for patients, often with debilitating and life-shortening diseases. These therapies may be targeted at individual patients and involve changing, replacing, or removing a patient's cells or genes. While such therapies present vast opportunities to provide innovative and highly personalized treatment options, they are also complex, costly, and time-critical to manufacture, which makes their use, and the conditions around such use, complicated.

Current difficulties

One area of particular difficulty is that such products often have a very short shelf life and require manufacture to take place at, or close to, the location where the patient receives treatment—this is known as point of care (PoC) manufacture. As these medicines are usually highly personalized to the individual receiving treatment, as is the case for autologous cell and gene therapies, this means that there may be multiple manufacturing sites for the product across different hospitals and clinics. Their supply therefore necessitates the *scale out* of manufacturing sites (adding more manufacturing sites), rather than the *scale up* of existing sites (increasing capacity to match patient need).

The manufacture and supply of these PoC products does not easily fit within the current UK legal framework relating to the development, manufacture, and supply of medicinal products, which focuses on medicinal products supplied under the standard model of factory-based manufacture. Notably, the manufacture of medicinal products is based on certification and inspection of each manufacturing site in compliance with GMP, which is impractical where there

are multiple individual hospital sites producing medicines at a patient's bedside. The current lack of a specific and clear framework for PoC manufacture has deterred many companies from manufacturing and bringing such products to the UK market. PoC medicines are, therefore, commonly provided as unlicensed medicinal products, referred to as 'specials' in the UK, which makes them incompatible with manufacture or delivery at-scale, and importantly, makes them harder for patients to access.

UK solution

The UK government has recognized this difficulty and the need for a legal framework to enable the proper and safe manufacture and use of these therapies in a bedside manner, whilst assuring appropriate quality, safety, and efficacy measures are maintained. The aim is to set out a framework to provide care that is flexible and tailored to individuals' needs and to increase the availability of novel advanced therapies across the UK.

INCOMING LAW ON PoC MANUFACTURE

On January 23, 2025, following consultation with numerous regulatory bodies, a new statutory instrument was enacted by the UK Parliament. Publicized as the first of its kind, The Human Medicines (Amendment; Modular Manufacturer and Point of Care) Regulations 2025/87 (the PoC Regulations [1]) are set to come into force on July 23, 2025. Further, the Medicines and Healthcare products Regulatory Agency (MHRA) has published a range of supporting guidance with additional details for companies seeking to take advantage of the new regime (Figure 1) [2].

The PoC Regulations define two sets of products as follows:

- **Point of care medicinal products** ('PoC medicinal products'), which are medicinal products that, for reasons relating to method of manufacture, shelf life, constituents, or method or route of administration, can only be manufactured at or near the place where the product is to be used or administered (which may include ATMPs derived from autologous therapies, blood products, and 3D printed products); and

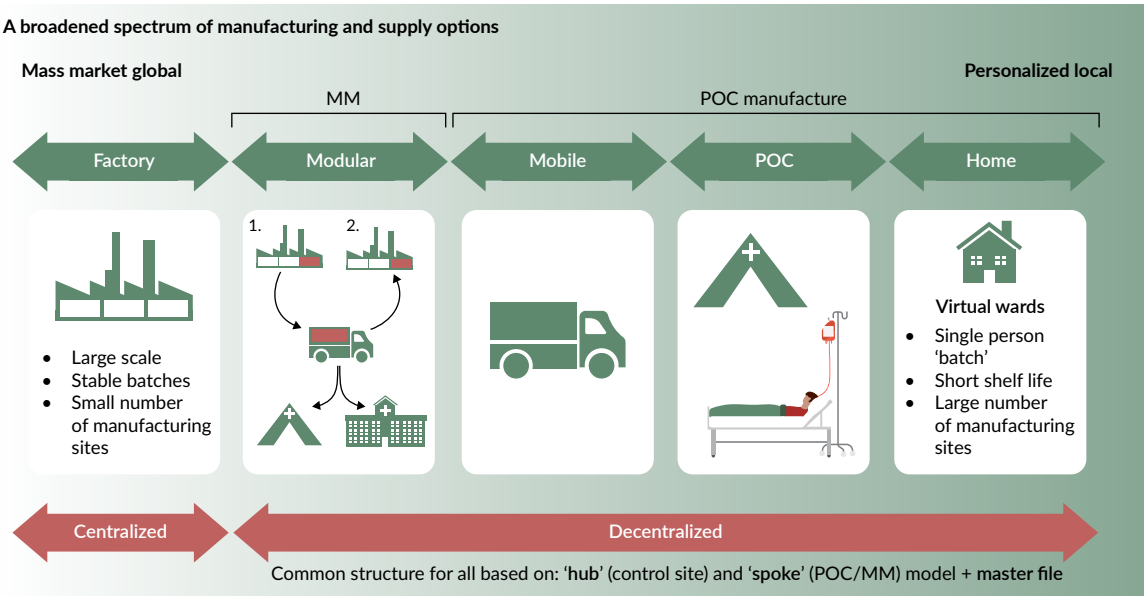
- **Modular manufacture medicinal products** ('MM medicinal products'), which are medicinal products that, for reasons relating to deployment, MHRA determines it necessary or expedient to be manufactured or assembled in a modular unit (which may include personalized cancer immunotherapy and manufacture of vaccines).

Below we set out an overview of the key concepts introduced by the PoC Regulations. Amendments have been made to both the Human Medicines Regulations 2012/1916 ('Human Medicines Regulations'), which set out a comprehensive regime for the authorization and regulation of medicinal products throughout their life cycle, and to the Medicines for Human Use (Clinical Trials) Regulations 2004/1031 ('Clinical Trials Regulations'), which govern the conduct of pre-authorization trials of medicines in the UK.

In this article, we focus on authorization of medicinal products, although similar amendments are made to both sets out regulations, and the precise requirements vary depending on whether the provisions relate to the authorized or clinical trial setting. Similarly, in most cases, the requirements for PoC medicinal products are described below, although similar requirements apply to MM medicinal products.

FIGURE 1

The PoC regulations provide a clear structure for the regulation of decentralized manufacture of a new range of categories of medicines as demonstrated in this MHRA infographic.



MHRA: Medicines and Healthcare products Regulatory Agency. MM: modular manufacture. PoC: Point of Care. Diagram based on [2].

WHEN DO THE PoC REGULATIONS APPLY TO ATMPs

The PoC Regulations bring PoC manufacturing sites under GMP, providing a flexible framework for the manufacture of ATMPs locally at the hospital. This is crucial for many ATMPs where there is a short shelf life and a need to minimize steps in the manufacturing chain. Importantly, the requirements of GMP are not relaxed, but the processes modified to enable flexibility in how they are applied to PoC manufacture.

As part of obtaining a manufacturing license, the applicant will need to set out how the relevant product is manufactured. Where there are reasons relating to the method of manufacture, shelf life, constituents, or method or route of administration, the product can only be manufactured at or near the place where the product is to be used or administered, the use of the PoC process can be applied. This is not necessarily a choice for the applicant, and the applicant will need to make an application for decentralized manufacture designation to the MHRA. The applicant will need to justify the need for a specific decentralized manufacturing approach against the relevant legal test, and provide supporting quality data, and where necessary, clinical data [3]. Therefore, if more standard manufacturing processes are possible, they should be used. Importantly, this process will not be available where the reason relates to convenience or costs alone; there must be other elements that mean PoC manufacture is required.

Therefore, while the PoC Regulations will be a welcome addition to the regulatory regime, it will not necessarily apply to ATMPs that are already authorized and therefore that already have a more standard manufacturing process in place. However, the hope is that the regime will mean more such products can be authorized and made available to patients.

STRUCTURE UNDER THE PoC REGULATIONS: HUB AND SPOKE

As set out above, a key difficulty with PoC manufacture is the sheer number of possible sites involved and that it is impractical under the current regime that each will be inspected and even named on the relevant licenses. To solve this process, the new UK framework is centered on a 'Control Site' concept: the Control Site is the location at which the holder of a manufacturer's license supervises and controls the manufacture or assembly of the medicinal product, whereas the PoC sites are the sites at which the manufacture or assembly of the PoC medicinal product physically takes place. MHRA guidance also sets out details of how this should operate and the systems that should be in place [4]. This process is similar to that of a 'hub and spoke' model used in the regulations of blood for transfusions and tissue and cell transplants, and establishes the decentralized PoC sites as the spokes, and the Control Site as the hub.

- **The Control Site:** the Control Site will be the only location named on the marketing authorization application of the PoC medicinal product and will provide the necessary controls on all aspects of the product manufacturing system
  - Key responsibilities of the Control Site include: the assessment and addition of new PoC sites; decommissioning PoC sites no longer needed; maintaining a strategy to ensure process performance and product quality; oversight of the quality system; training; provision and control of manufacturing equipment; maintenance of traceability information; audits of PoC sites; and implementing a system to capture incidents, breaches and adverse events
- **The PoC site:** physical manufacture will be devolved to the PoC sites, as named in the product's master file
  - The MHRA does not intend to inspect each PoC site but will consider the processes set out in the master file and likely conduct spot checks of sites to ensure the processes and oversight are operating as stated
  - Relationships with hospitals and treatment centers will be key to ensure they can meet the requirements for each product. However, it will be important to ensure that processes can be implemented on the ground, as if a hospital is a PoC site for many products, there will likely need to be some commonality between the various systems
- **The master file:** key to the operation of the PoC Regulations is the master file, which sets out a detailed description of the arrangements for the manufacture or assembly of the relevant PoC medicinal product. This concept is not new and has been adapted from existing regulations (for example, active substance master files)
  - The master file will need to be kept up to date as changes occur and supplied to the MHRA on a routine basis for review and assessment. This will require detailed processes and systems to document and evidence changes
  - Oversight of the Control Site will be performed by a qualified person. The master file must set out how the qualified person will have oversight of the PoC sites and ensure appropriate release of the product, how it is recorded and the records that will be put in place

KEY REQUIREMENTS UNDER THE PoC REGULATIONS

The PoC Regulations make various amendments to the Human Medicines Regulations and Clinical Trials Regulations to take into account the unique nature of such products. We set out some of note below:

- **Manufacturing license** [4]**:** it remains the case that the relevant medicinal product must be manufactured or assembled in accordance with a manufacturer's license and GMP. The PoC Regulations set out that this should also be undertaken in accordance with the relevant master file for the PoC medicinal product
  - Applications for a manufacturer's license must be accompanied by a dossier for each PoC medicinal product, which provides details such as location of operations, descriptions of processes and reporting requirements, and contact details of relevant personnel. This will take account of unique considerations relating to the products, such as the 'on demand' nature of PoC medicinal products
  - Once granted, the PoC medicinal product specified in the manufacturer's license must be handled, controlled, stored, or distributed on the Control Site or PoC site, and as specified in the master file
- **Marketing authorization applications** [5]**:** where made, marketing authorization applications for a PoC medicinal product (including for ATMPs) must be accompanied by the relevant master file for the product (along with all other accompanying material, as required under the Human Medicines Regulations)
  - As noted above, the marketing authorization will only name the Control Site, but the master file will set out the information on PoC sites and control and oversight of such sites
  - It must be ensured that the manufacturer's license and the master files are consistent with a marketing authorization relating to the product at all times
- **Pharmacovigilance requirements** [6]**:** the holder of the manufacturer's license should record and report all suspected adverse reactions linked to the product to the marketing authorization holder, and an appropriate pharmacovigilance system must be put in place
- **Packaging and labelling** [7]**:** packaging and labelling requirements apply only if the PoC medicinal product is not administered in its entirety immediately after manufacture. Otherwise, packaging and labelling requirements specific to PoC medicinal products must be complied with, which are similar to the requirements in place under the Human Medicines Regulations

POSITION IN THE EU

The position in the EU on PoC and modular manufacture is not clear-cut. Currently, only high-level considerations are set out in guidance (for example, in the European Commission's 2017 guidance on GMP specific to ATMPs [8] and the recently published Guideline on quality, non-clinical and clinical requirements for ATMPs in clinical trials [9]) and there is no specific regulatory framework governing decentralized manufacture. This means that in practice, decentralized manufacture does not take place.

However, there have been some discussions about decentralized manufacturing

within the EU institutions. The EU is currently considering a wholescale update to the regulation of medicinal products. The European Commission's proposal [10] highlighted the need for an EU regulatory framework that shifts away from existing structures designed to meet the expectations of large-scale manufacture. It set out that the proposed new framework should incorporate a "*risk-based and flexible approach that will enable the manufacture or testing of a wide range of medicinal products in close proximity to the patient*." A central site concept, similar to that of the Control Site concept adopted in the UK, was proposed to oversee decentralized sites. It is proposed that decentralized manufacture should be conducted under the responsibility of a qualified person of an authorized central site, with oversight of the decentralized sites, in a similar manner to that advanced in the PoC Regulations. Further, the decentralized sites should be registered by the competent authority of the Member State in which the decentralized site is established.

The European Parliament [11] made minimal changes to these proposals, although emphasized the need for coordination between the authorities. The European Council also made some proposed amendments to the draft framework [12,13], though the general concept as proposed by the Commission remains the same. Changes specify that a request for approval should be made within a marketing authorization application for use of decentralized manufacturing and the proposed amendments provide more prescriptive provisions on specific details that must be included in a manufacturing authorization application for a central site.

Crucially, however, it is currently unclear to what extent the new legislation will be approved and/or modified by the EU institutions as part of the trialogue discussions that are ongoing at the time of writing, and when the final legislation will come into force. This could take several years and therefore it may be some time before we see any significant and substantial legislative changes in the EU.

In addition, the International Coalition of Medicines Regulatory Authorities (ICMRA) has also considered these issues, and a workshop took place in December 2024 on decentralized or distributed manufacturing [14]. We understand that the ICMRA and relevant international regulatory organizations will develop regulatory guidance on this area, which will hopefully lead to harmonization of these requirements across jurisdictions, and could lead to changes to the UK legislation and guidance in the future.

CONCLUSION

The implementation of the PoC Regulations is a big step forward by the UK and recognizes the fact that as scientific and medical advances are made in the development of more complex and personalized treatments, such as cell and gene therapies, a one size fits all regulatory regime is no longer suitable or sustainable. The UK is at the forefront of making legal changes to allow more PoC products, including ATMPs, to be supplied to patients, while maintaining their quality and safety. The hub and spoke structure of the proposed regulatory regime has proven successful in other areas of regulation; however, nuances applicable to cell and gene therapies, such as short life span, use of autologous vs allogeneic human samples, and the specificity of treatment, must be considered and the master file must set out detailed provisions on how these factors will be controlled. This means that the MHRA will need to ensure that, and indeed has acknowledged that, the guidance accompanying the PoC Regulations will be adaptable, to allow the regime to work successfully and evolve over time to meet future needs.

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AUTHORSHIP & CONFLICT OF INTEREST

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