

Regulatory Insights

COMMENTARY/OPINION

The UK's emerging regulatory framework for point-of-care manufacture: insights from a workshop on advanced therapies

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Point-of-care (POC) manufacture can be defined as the production of therapies in clinical settings or units close to hospitals and patients. This approach is becoming increasingly viable due to the emergence of flexible manufacturing technologies. Expecting an increase in this kind of production, the UK's regulatory agency, the Medicines and Healthcare products Regulatory Agency (MHRA) is proposing a regulatory framework specifically designed for POC manufacture. To discuss the challenges of POC manufacture and the MHRA's proposal, the EPSRC Future Targeted Healthcare Manufacturing Hub (FTHMH) organized a workshop drawing insights from specialists in cell and gene therapy manufacture. Through presentations and discussion roundtables, the workshop highlighted the challenges for the UK and other countries implementing POC manufacture. The workshop attendees stressed four main issues: quality control; standardization and equipment use; availability of qualified personnel; and the challenges to be met by hospitals participating in POC manufacture systems. This commentary provides a summary of the points discussed in this workshop.

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**CONTEXT: MANUFACTURING
ADVANCED BIOTHERAPEUTICS**

Academic institutions and companies have for some years developed personalized cell and gene therapies [1,2], also called Advanced Therapy Medicinal Products (ATMPs), such as CAR-T cell therapies. At the same time, new manufacturing equipment has been developed to optimize ATMP production [3-5]. It is sometimes claimed that these trends enhance the prospect of bringing manufacture close to the patient, but it is also recognized that several operational, regulatory, public policy, and healthcare challenges remain for this to become routinely used.

Traditionally, drugs and therapies have been produced in a centralized manner, with a small number of large manufacturing units strategically positioned across the globe [6]. With newer, flexible, and automated equipment, it becomes increasingly possible to achieve decentralization that could lead to a larger number of manufacturing units located close to hospitals [4]. In some cases, it might be possible to perform manufacturing activities within the hospital, constituting so-called point-of-care (POC) manufacture. In some countries, ATMPs have been manufactured at POC, which has involved, for the most part, production of therapies to be tested in clinical trials. However, there is already a small group of hospital-based clinicians/researchers producing biotherapeutics for routine clinical procedures in dedicated Good Manufacturing Practice (GMP) manufacturing facilities. For example, mesenchymal stem cells have been manufactured at the Mater Hospital Brisbane (Australia) for the treatment of acute myeloid leukemia [7]; and red blood cells have been produced by NHS Blood and Transplant (UK) for treating cardiac illnesses [8]. In some cases, such production involves the use of miniaturized manufacturing systems (so-called GMP-in-a-box) which can sometimes be transferred from hospital to hospital.

ATMPs have short shelf lives when delivered fresh, that is, they have to be administered to the patient promptly after their manufacturing process has been completed.

This is a major reason why hospitals, health services, and some companies are becoming interested in bedside manufacture.

Since freshly delivered ATMPs have these particular characteristics, it has been challenging to formulate and implement regulations to frame their development and production [2,9]. The decentralization of production, the emergence of new manufacturing platforms, and particularly the conduct of POC manufacture in a large number of hospitals, bring about additional regulatory challenges, as regulatory agencies need to learn to ensure the continued safety, efficacy, and quality of medicinal products manufactured outside centralized facilities.

These regulatory demands have been felt in many countries, particularly those willing to offer a dynamic landscape for the development of ATMPs, like the UK [10]. The Medicines and Healthcare products Regulatory Agency (MHRA), the UK's regulatory agency, has paid much attention to these trends. For example, in a recent partnership with the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC), the MHRA launched the Innovative Licensing and Access Pathway (ILAP) [11], a new regulatory route aimed to speed up the marketing authorization of chemical entities, biological medicines, and repurposed medicines.

POC manufacture has also been on the MHRA's radar. In a recent application submitted to the agency, the applicant plans to manufacture a blood product at POC, in a system that will involve over 200 hospitals. To deal with this application, and similar ones, a new approach has to be created for managing risks, ensuring quality control, and tracking liabilities. For this reason, the MHRA is now proposing a new regulatory framework specifically designed for POC manufacture. This is done in the framework of the 2021 Medical Devices Act, which allows for regulatory divergence between the European Union and the UK after the UK departure from the Union.

To develop the POC regulatory proposal, the MHRA initially consulted specialists in medicines manufacture, by means of three

workshops held in 2020–2021. It was then possible to identify the main issues to be dealt with in POC manufacture systems [12]:

- ▶ Frequent production of autologous therapies, which are custom-made therapies whose starting material is constituted by samples taken directly from the patient;
- ▶ Production of small batches; frequently, a batch is formed of only one product for a particular patient;
- ▶ The shelf life of products (that is, the period for which products remain active and safe) are either short, amounting to seconds in some cases; in this way, it is not viable to have the manufacturing units located far away from the patient;
- ▶ The manufacturing system can involve several units, hospitals or even mobile units such as adapted vehicles; this circumstance poses considerable challenges in terms of inspection of manufacturing sites; and
- ▶ Depending on the skills and the infrastructure that is available, different units of the same manufacturing system might need to employ different techniques, devices, or software packages.

It was noted, therefore, that current regulatory schemes that might be used in POC manufacture (such as the Specials scheme [13], which is applicable to unlicensed therapies produced for special clinical needs) are not completely suitable for large POC manufacturing systems. The MHRA has then designed a new regulatory framework which was initially presented in an online workshop in March 2021. After receiving feedback from the specialists who attended this event, the MHRA released, in August 2021, a public consultation.

This Commentary aims to provide an overview of the MHRA's framework regulatory proposal and, subsequently, summarize

the discussions that took place in an online workshop organized by the Future Targeted Healthcare Manufacture Hub (FTHMH) [14] hosted at University College London. Held on 29 June 2021, with talks by Ian Rees (MHRA), Dr Qasim Rafiq (FTHMH), and Laura Sands (Lonza), as well as several breakout sessions, our workshop provided a space for the expression of insights and concerns about POC manufacture and the MHRA's regulatory framework proposal from the viewpoint of ATMP manufacture, delivery, and administration.

THE MHRA'S REGULATORY FRAMEWORK PROPOSAL

Given the issues described above, the MHRA aims “[...] to establish a proportionate regulatory framework that supports the safe development of medicines which need to be manufactured and supplied in close proximity to patients or new supply chains that enhance patient access” [12].

It is important to note that the emerging regulatory framework does not focus on any particular class of products and can therefore impact on “[...] a wide range of POC product types including blood products, medical gas products, Advanced Therapy Medicinal Products (ATMPs) and small molecule products” [12]. In order to enable the formation of manufacturing systems that may comprise a large number of sites while making sure that quality control is always in place, the MHRA proposes the concept of Control Site. This will be the institution responsible for establishing and overseeing the POC manufacturing process, with responsibilities that will include: staff training, quality control, provision of manufacturing equipment, adverse event reporting, auditing of manufacturing sites, and others. The Control Site will take the product from the development phase to the market, which will comprise securing a clinical trial authorization, conducting the clinical trial, and obtaining a marketing authorization.

The Control Site will oversee the Manufacturing Sites, which will be, for the most part, NHS hospitals and, in some cases, manufacturing units located close to a hospital or a mobile manufacturing unit installed, for example, in an adapted vehicle. As Manufacturing Sites may be in large numbers, one of the main challenges is to ensure consistent quality across the whole production system. Precise and timely communication will then need to be in place between the Control Site and Manufacturing Sites, including for the notification of adverse events, by means of a reporting system to be created by the Control Site. When the product involves high risks, such communication may need to happen in real time.

All the information pertaining to the manufacturing system will be stored in a POC Manufacture Master File. This kind of document has been used in other fields, such as for plasma and vaccine production. In POC manufacture, the Master File will be more flexible, as its contents and the frequency of its update will depend on the product's nature and associated risks. The POC Master File will contain information about: GMP

inspections; staff; adverse events; batches; patients receiving the product; participating sites, among other items.

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 [15]**.

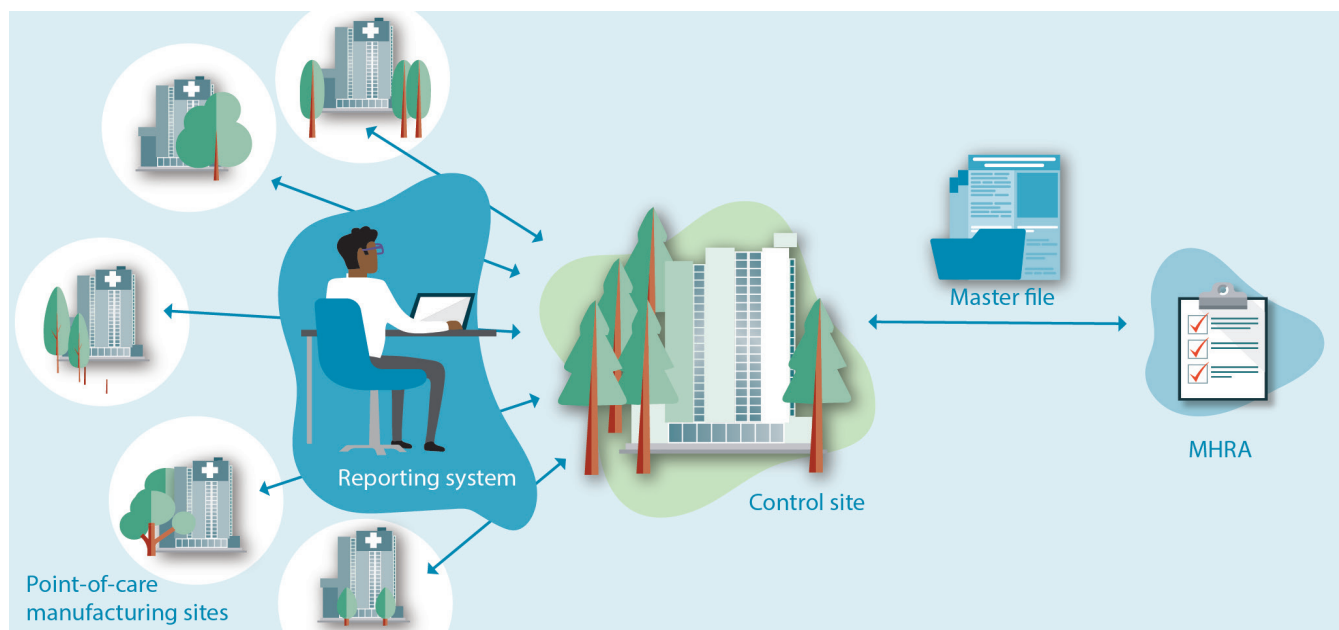
Due to the variety of products to be covered by the emerging regulation, as well as the diversity of players that may be willing to manufacture products at POC, it is crucial that the framework be proportionate, flexible, and able to accommodate various manufacturing systems, with either a small or large number of Manufacturing Sites. Thus the MHRA will be open to adjust some aspects, such as the contents of the POC Master File and the frequency of Manufacturing Sites inspections.

THE WORKSHOP ON POC MANUFACTURE

The Future Targeted Healthcare Manufacture Hub (FTHMH) held an online workshop

FIGURE 1

A schematization of the MHRA's regulatory proposal.



Created with BioRender. Source: [15].

on 29 June 2021 with two goals: to discuss the current scientific, technical, institutional, and regulatory challenges of POC Manufacture; and to collect feedback on the MHRA's regulatory framework proposal, based on the example of ATMP manufacture, delivery, and administration. The workshop convened 32 specialists in the field of biotherapeutics, manufacturing technologies, and regulation, as summarized in **Figure 2**.

As an initial activity of the workshop, participants were polled on what they considered to be the most challenging aspect of POC manufacture to be tackled in the next years. The responses we received are summarized in **Figure 3**.

According to these responses, the main challenge to be dealt with is "Equipment and infrastructure" (40% of participants), followed by "Qualified personnel" (35%). This is reflected in the comments that participants made about the MHRA's proposal, as explained below. It is interesting to note that 20% of participants selected "Regulation," in line with the MHRA's diagnostic that a new regulatory framework is needed to foster POC manufacture at this moment.

Three keynote presentations were given in the workshop. Ian Rees (MHRA) presented the agency's POC regulatory framework proposal, its concepts, guiding principles, and implementation structure. Dr Qasim Rafiq (FTHMH) addressed technical and scientific

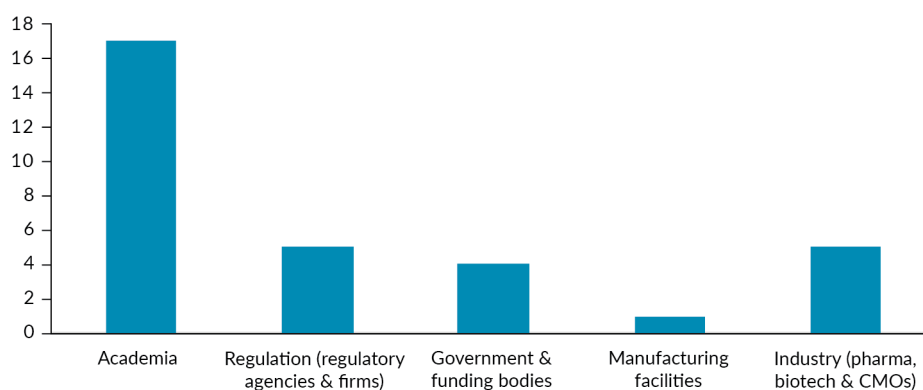
issues in the decentralization of advanced biotherapeutics manufacture, including POC manufacture more specifically, and emphasizing the growing relevance of highly automated production systems. Subsequently, Laura Sands (Lonza) described the company's approach to technology development for manufacture decentralization, highlighting the potentialities of the Cocoon© system and its possible use for cell therapy manufacture in clinical settings. Presentations were followed by discussion roundtables. The sections below provide a summary of the main points and discussions made in our workshop, focusing mainly on participants' views about the MHRA's POC regulatory framework proposal.

SUMMARY OF WORKSHOP DISCUSSIONS

Generally, workshop attendees expressed a positive view about the MHRA's POC regulatory proposal. The concept of Control Site and the flexibility of the framework (that is, the willingness to adjust the regulatory oversight to different kinds of products and manufacturing systems) were particularly welcome by participants. However, they also raised several issues to be further considered by the regulator. Below we highlight the issues that emerged the most frequently in the

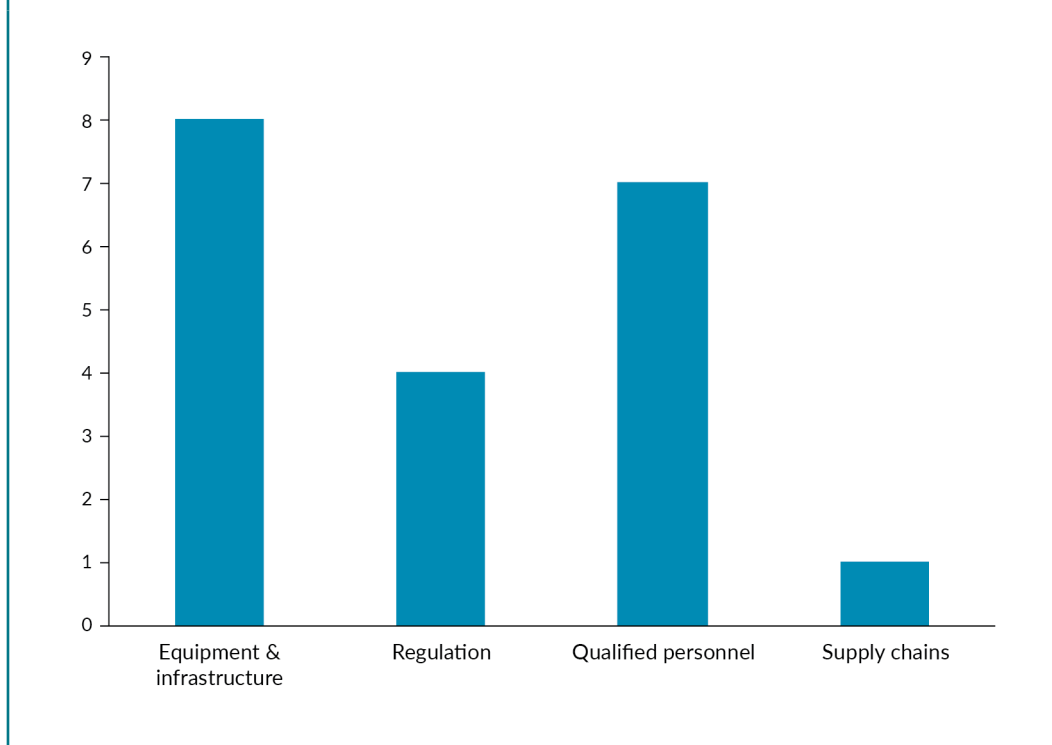
► **FIGURE 2**

Affiliation of workshop attendees.



▶ **FIGURE 3**

Survey responses on hardest challenges of POC manufacture.



breakout sessions, pointing to some aspects that deserve further refinement and consideration. In order to outline all the discussions in a systematic way, this section focuses on four main themes as they were addressed in the workshop: quality control; equipment and standardization; human resources and training; and implementation in hospital sites.

Quality control

When production is centralized and involves few manufacturing units, it is relatively simple to perform equivalent control measures. However, this practice may be compromised in a more decentralized system, and even more so if large numbers of manufacturing sites are employed. The main challenge is that small procedural changes may be implemented at each site, either consciously or unconsciously.

Workshop participants stressed, for example, the issue of software updates. If different Manufacturing Sites implement updates independently, minimal variations will be introduced in manufacturing systems that are

likely to rely on software support for a growing range of tasks. To minimize the chance of discrepancies, it will be crucial to have data integrity approaches, automated software updates, and continuous monitoring.

Another challenge in terms of quality control is the broad range of materials to be handled and processed in POC manufacture. This makes it difficult to decentralize all aspects of quality control. Some workshop attendees pointed out that some Control Sites may prefer to test and approve some materials in a centralized fashion, subsequently releasing them for use in clinical settings.

Participants also expressed doubts about the role to be played by Qualified Persons (QPs), who are professionals responsible for assuring the quality of medicines and certifying batches. 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. This type of monitoring will only be viable with highly automated manufacturing systems and, ideally, real-time monitoring,

but it will be necessary to wait until such technologies are available.

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. The MHRA explains that the File's information can be used along the path leading to product registration and marketing authorization. It will then be important to have timely guidance about such process.

Equipment & standardization

In the UK, some initiatives have supported the development and implementation of ATMP manufacturing technologies, as is the case of the Advanced Therapy Treatment Centres network [16]. It is not certain, however, that such technologies will be evenly diffused across regions and hospitals. Variability between Manufacturing Sites can then become a key challenge of POC manufacture. Indeed, hospitals have different infrastructures and staff with varied experience in ATMP production, and quality control. It is known that some NHS Trusts have devoted themselves to therapy manufacture, including some with experience in the production of cell therapies. At the same time, there are Trusts whose pharmacies have much more modest manufacturing skills and capabilities. This variability can be solved, or at least minimized, by means of closed, automated systems, in such a way that mobile manufacturing units (GMP-in-a-box) are taken to hospitals whenever certain products are necessary. If the newest technologies are mobilized, it can be possible to manufacture therapies at POC with little need for manipulation of materials and products and, consequently, little need for having highly trained staff.

According to workshop participants, then, some risks of POC manufacture can be reduced with technological solutions. In our event, examples were provided of such

solutions. According to Laura Sands (Lonza), the Cocoon[®] system for cell manufacture is flexible enough to be used in various settings, including clinical ones. And Dr Qasim Rafiq (FTHMH) presented Autostem, a project led by the National University of Ireland Galway and aimed to develop an automated system for stem cell manufacture. Even if such a system is used in regional manufacturing hubs, and not exactly at POC, it can enable a precise production with less occurrences of human errors.

Another key issue is the level of investment needed for setting up those manufacturing systems. With devices incorporating cutting-edge technologies, and with small numbers of providers on the market, automated manufacturing platforms can be costly. In addition, technologies will be necessary for implementing data integrity systems and monitoring site variability, as mentioned above. The financial schemes that will enable the deployment of such technologies to hospitals are not yet clear. Furthermore, some POC manufacture systems may involve a large number of sites, compounding these financial challenges.

Therefore, the workshop discussions are in line with considerations that had been voiced before [17], namely: the feasibility of POC manufacture will depend on the number of sites and the reimbursement models agreed upon with hospitals.

Qualified personnel

Even with highly automated systems in place, it will be necessary to rely on a range of professionals. For example, QPs will be crucial players for assuring quality control, as explained above. In addition, other professionals must be mobilized for tasks such as: materials handling; pre-process checks; manufacturing device operation; documentation and regulatory compliance; and coordination of the different players and departments involved.

Training of such personnel was stressed as a key enabler for POC manufacture by

workshop participants. The MHRA's regulatory framework proposal includes training as one of the responsibilities of the Control Site. It might be relatively easy to devise training schemes for staff related to the Control Site. However, if hospital staff are to participate in manufacturing activities, then those individuals will need to undergo training as well. To be sure, the Control Site can design training programs to be rolled out across various Manufacturing Sites. However, this brings about the challenge that was pointed out above for quality control: how to make sure that such training is implemented in a standardized way, with no significant variations between different sites. These issues are particularly relevant when one considers that manufacturing technologies are likely to evolve constantly and rapidly in the years to come, which will require frequent re-training of the involved personnel.

If participation of clinical staff in POC manufacture is at least considerable, then it is important to understand what the incentives for such participation will be. Hospital employees are frequently very busy with their routine medical and administrative tasks. Some workshop participants pointed out that in these conditions, additional training and manufacturing duties may end up being of little interest. They also argued that when the product at stake is not manufactured frequently, then there may be little incentive to acquire these new skills. This is particularly problematic for ATMPs, as some of them will target rare diseases with small, or very small, patient populations. Therefore, the issues of mobilization of staff, training, and workforce maintenance become pressing questions, as they can have decisive impacts on the final product's quality.

Hospitals

For hospitals, it may be too challenging to follow all the guidelines involved in therapy production, especially the very strict GMP standards complied with by the industry. For

some classes of products, including ATMPs, sophisticated processes will be necessary, such as the work with complex materials and the management of large supply chains which will frequently have an international scope. In clinical and academic settings, this expertise is often lacking [18,19], and it is not sure that it can be implemented without much initial effort.

As explained before, some ATMPs will target small patient populations. This may be a deterrent to some hospital administrators unable or unwilling to reserve resources, physical space, and staff for activities who do not seem beneficial to many patients. In some cases, then, it can be more useful to concentrate certain manufacturing activities in some strategically selected hospitals, which will produce for a relatively larger number of patients. This solution may also help solve the training difficulties described above.

The financial aspect of POC manufacture was also discussed by workshop participants. Hospitals may be asked to reimburse the sponsor company (or drug developer) for manufacturing activities happening on their premises. Alternatively, the hospital may receive part of the therapy's reimbursement, as is done in the MHRA's Specials scheme for unlicensed medicines. For companies, manufacturing schemes can prove less attractive if the hospital receives a significant portion of the reimbursement.

Finally, an issue that is likely to become crucial is distribution of liabilities between POC Manufacturing Sites and the Control Site. As noted above, there may be deviations from the original manufacturing protocol, bringing about additional and unforeseen risks. It will then be essential to receive specific guidance from the MHRA, so it is possible to know who is technically and legally responsible in manufacturing processes and systems that can reach high degrees of complexity.

Given that hospitals will play a crucial role as Manufacturing Sites, these issues need to be attended to. Otherwise, it is not guaranteed that the regulatory proposal will act as an enabler for POC manufacture as it is intended to do.

THE FUTURE OF POC MANUFACTURE IN THE UK

It has been claimed that current technological trends require “[...] smarter, more adaptive regulatory systems [...] that are more proportionate to the levels of risk embedded in new technologies” [20]. Equally, it has been noted that emerging therapeutic approaches, such as cell and gene therapies, require “pioneering regulatory development” [21]. The MHRA’s POC regulatory framework proposal seems to be in line with these considerations, as it brings about a regulatory approach aimed to be innovative, flexible, and proportionate. The flexibility of the proposed framework was indeed praised by our workshop attendees. Furthermore, the MHRA has been considerably successful in its dialogue with therapy manufacturers. This experience will likely be valuable in the years to come because, as noted before [22], ongoing dialogue between regulators and manufacturers is key when it comes to producing ATMPs at POC.

It is expected that the emerging regulatory framework will be approved by the end of 2021 or in the beginning of 2022, after completion of the public consultation and the Parliamentary process. When it becomes law, it can provide additional incentives for POC manufacture in the country, an MHRA’s expectation. At the same time, the important challenges entailed by such expansion of POC manufacture, some of which have been highlighted in this Commentary, need to be considered. They manifest themselves at a very

particular historical moment, after the legal transition represented by Brexit and the unprecedented medical demands generated by the Covid-19 pandemic. These circumstances make it particularly important to combine technical and medical requisites harmoniously or, differently said, to seek “[...] the right balance between following the hospital internal rules and directives and putting in place procedures in order to meet GMP and GCP compliance” [22].

On the one hand, it is important to go beyond the present situation, in which POC manufacture depends on solutions found or improvisations made in particular hospitals, with low levels of collaboration and technology diffusion [23]. On the other, it is also necessary to pay attention to the concentration of technical expertise or controlling force that may derive from highly standardized manufacturing systems.

Our workshop attendees believe that these challenges can be surmounted, and these potentialities fully explored, if the issues discussed above are properly attended to in an open, responsible, and continuous manner. To a large degree, this view is shared by the members of our FTH Manufacturing Hub who have conducted studies on several aspects of POC manufacture. With the continuation of such and similar discussions and research projects, the UK can become a pioneering country not only in terms of regulations for POC manufacture but also in terms of actual production of useful therapies in clinical settings.

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AUTHORSHIP & CONFLICT OF INTEREST

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