Research Article

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Institutional and infrastructure challenges for hospitals producing advanced therapies in the UK: the concept of 'point-of-care manufacturing readiness'

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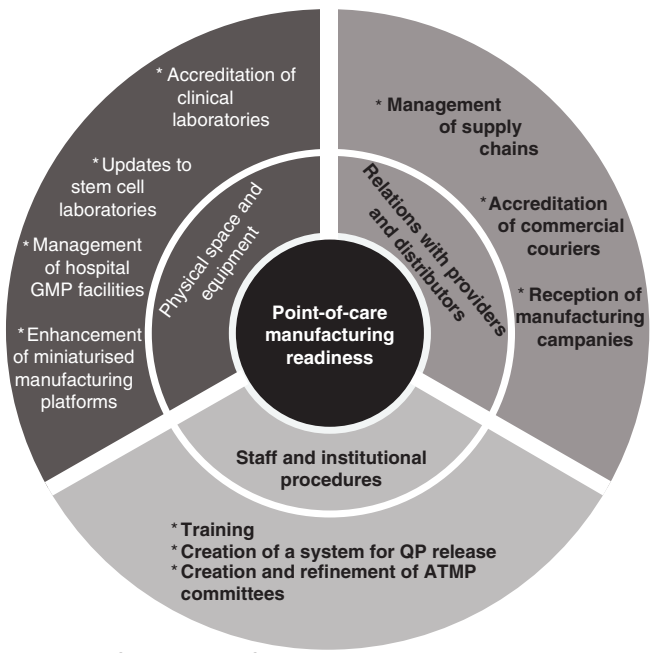
Aim: To propose the concept of point-of-care manufacturing readiness for analyzing the capacity that a country, a health system or an institution has developed to manufacture therapies in clinical settings (point-of-care manufacture). The focus is on advanced therapies (cell, gene and tissue engineering therapies) in the UK. **Materials & methods:** Literature review, analysis of quantitative data, and qualitative interviews with professionals and practitioners developing and administering advanced therapies. **Results:** Three components of point-of-care manufacturing readiness are analyzed staff and institutional procedures, infrastructure, and relations between hospitals and service providers. **Conclusion:** The technical and regulatory experience that has been gained through manufacturing advanced therapies at small scale in hospitals qualifies the UK for more complex and larger-scale production of therapies in the future.

Graphical abstract:



Point-of-care manufacturing readiness, its components and its challenges

Plain language summary: Point-of-care manufacture is the production of therapies in hospitals, carried out when there is no time for storing the medicine, which is delivered to the patient with no delays. Such procedures can be useful for advanced therapies derived from techniques such as gene editing, cell manipulation and tissue engineering. Over the last decades, UK hospitals have produced advanced

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therapies in small quantities. In the future, this production will likely be more thoroughly integrated into clinical routines. In this way, the technical and regulatory experience that hospitals have accumulated so far underpins the more frequent and larger-scale work expected for the future. This accumulation of expertise, infrastructure and institutional contacts provides the foundation for what we call 'point-of-care manufacturing readiness'.

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Keywords: advanced therapy medicinal products (ATMPs) • hospital exemption • institutional readiness • point-of-care manufacture • point-of-care manufacturing readiness • regulation

The concept of point-of-care manufacturing readiness in advanced therapies

Over the last decade, a trend has been observed whereby the production of therapies is slowly taken to the hospitals and clinics where patients are treated. As this trend is consolidated, capacity needs to be built, because considerable challenges will be faced by caregivers, therapy manufacturers, and regulators. In order to highlight these issues, this paper focuses on the emerging domain of personalized medicine, proposing the concept of 'point-of-care (POC) manufacturing readiness'.

The notion of manufacturing readiness began to be conceived in 1974 when NASA proposed the idea of technology readiness levels to measure the maturity of certain technologies [1]. "*However, the readiness of a technology does not necessarily indicate that the related products are ready to be manufactured in an affordable and operationally effective manner*" [2]. To fill this gap, the US Department of Defense then introduced the idea of manufacturing readiness levels. At the most mature stage, or at the highest readiness level, "*All materials, tooling, inspection and test equipment, facilities and manpower are in place and have met full rate production requirements*" [3].

If initially the idea of manufacturing readiness had this highly technical, strategic and military connotation, it has gained a more neutral tone across the decades, being applied to a large range of technology fields. Recently, the idea reached the biomedical area, being mobilized to assess the maturity of drug development [4] and vaccines [5], and even more complex domains such as bioprinting [2] and stem cells [6].

Here we propose further broadening this approach by considering that technologies generate therapeutic products not only when their level of technical development is high but also when there are appropriate regulatory and institutional environments for safe and effective manufacture to be carried out. This conceptual expansion is particularly useful when it comes to analyzing products whose manufacture needs to happen in institutionally delicate settings. This is the case of so-called 'POC manufacture'.

It is assumed here that POC manufacture is performed whenever a therapy, instead of being produced in a specialized unit, is manufactured in a hospital (or at least in a unit close to the hospital). This production model tends to be appropriate for some products, including advanced therapy medicinal products (ATMPs), understood as therapies derived from gene editing, cell manipulation or tissue engineering, or a combination of these. These therapies must be produced in line with GMP and are said to enable medicine personalization, with therapies being made to fit patients' needs and biological features [7,8]. The UK has been in the forefront of ATMP development, which has led to the preparation of studies and checklists focusing on the utilization of these products in UK hospitals [9]. The present study also wishes to advance in this direction – even though we adopt a more interpretive, less applied approach – and focuses specifically on the capacity to manufacture ATMPs.

We are dealing with products made of fragile and short-lived structures such as pancreatic islets, which "*have a finite lifespan and cannot be readily stored or cultured for long periods of time, although certain exceptions exist*" [10]. The therapies produced with such structures end up having short expiry dates, making it necessary to perform manufacture in hospitals [11]. Indeed, the short shelf life of therapies is one of the main justifications for their POC manufacture, as we have explained elsewhere [12,13]. An additional key reason is the difficulty associated with the transport of such perishable products [14]. It has been explained that manufacturing ATMPs in hospitals "*significantly reduces the cost and complexity of the logistics required to deliver personalized medicines to patients, while in parallel decreasing the risks to the product's integrity and cellular product quality associated with product transport over long distances*" [15].

Therefore, POC manufacture is likely to be necessary at least for some ATMPs. Some organizations are already trying to routinize this kind of production. Public institutions have had successful outcomes, as is the case for the

Sheba Medical Institute in Israel, which has managed to produce a therapy against cancer in shorter times than the industry [16], as well as the University Hospital Lausanne (Switzerland), where clinicians are manufacturing therapies for severe burns, a disease area generally neglected by the industry [17]. A few companies are also designing the first business models for POC manufacture. For example, CellPoint in The Netherlands is using a miniaturized manufacturing equipment to produce a therapy against cancer in hospitals endowed with some local manufacturing capacity, wishing to deliver a more affordable therapy in this way (https://cellpoint.bio/).

So far, regulatory agencies have considered the production of therapies in hospitals as an exceptional case, and have therefore overseen it by means of regulatory exemptions. In the EU, the EMA has used the so-called hospital exemption [18–20], a regulatory scheme that enables clinicians to produce bespoke therapies at very small scale to treat specific patients. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has used the so-called Specials scheme, which is similar to the EU exemption but provides clinicians with some additional flexibilities [21–23]. However, these schemes are now proving limited in scope, as POC manufacture is expected to be practiced more widely and frequently, making regulators feel the need for more specific frameworks.

One of the pioneers in this process is the MHRA, which has proposed a new regulatory framework specifically designed for POC manufacture [12,13]. It will be seen that for some players, the new manufacturing models announced by the MHRA framework proposal represent an upheaval in therapy production, requiring, for example, that hospitals learn new ways to work. Indeed, taking manufacturing activities to a hospital is not straightforward [24], as a series of material requisites need to be met, including the existence of some facilities where it will be possible to perform "*product development, product manufacture, quality control testing and in parallel to establish a pharmaceutical quality system compliant to laws and regulations*" [15]. As a result, at the international level, there are only a few hospitals where ATMPs are manufactured [25]. These difficulties are compounded in countries with relatively modest economies such as Chile [26] and Ethiopia [27].

Nevertheless, more dynamic countries such as Spain and the UK are better positioned due to their frequent participation in international clinical trials, generating much familiarity with standards mandated by the industry [28]. Furthermore, as will be seen below, there is, from an institutional point of view, some common ground between current ATMP manufacturing activities under the Specials regulatory scheme, on the one hand, and the new manufacturing models announced by the UK's emerging framework on the other. Indeed, the current small-scale ATMP production taking place in hospitals has generated technical, regulatory and institutional expertise that will be most useful when POC manufacture is practiced in more routinized ways. It is in this sense that we propose the concept of 'POC manufacturing readiness'.

Our analysis draws mainly on information from British institutions, but the concept can shed light on similar situations in other countries, guiding those willing to analyze how prepared countries and health systems are to receive and foster manufacturing activities in their hospitals. What is proposed here is not a quantitative measure such as the one found in analyses based on the idea of manufacturing readiness levels; rather, the present study aims to capture some signals indicating the extent to which a healthcare system is endowed with the skills and resources necessary for more robust and widespread activities in ATMP POC manufacture. In this way, the proposed concept can be understood as an extension of the idea of institutional readiness [29].

This paper is organized as follows. After reviewing our research methods, we set out to outline the current situation of ATMP production in UK hospitals. Three aspects of POC manufacturing readiness (staff and institutional procedures, infrastructure, and transportation) are then analyzed, and the main challenges faced by hospitals pointed out. We then focus on some important implications of the concept proposed here, followed by some closing remarks.

Research methods

This study was conducted in University College London. Its main goal was to understand key regulatory and institutional challenges in the development and production of ATMPs, with special attention given to the emerging domain of POC manufacture. Our research methods were reviewed and approved by the Research Ethics Committee of our university. In addition to a literature review on challenges in ATMP development and POC manufacture, three groups of methods were mobilized.

First, qualitative semistructured interviews were carried out with professionals involved in the development and delivery of ATMPs, as summarized in Table 1.

These 34 interviews explored the interviewees' professional and personal perceptions of the development and regulation of ATMPs, as well as prospects for their POC manufacture. For analysis, we coded different parts of the

Table 1. Professionals interviewed: April 2021 to March 2022.[†]

Category	Interviewees
Hospital staff	11
Researchers based in universities or research centres	8
Companies	5
Regulatory or government agencies	4
Regulatory advisers for private companies	4
GMP manufacturing facilities of public institutions	2
Total	34

[†]An extended version of this table, with information for each interviewee, is provided in Table 4.

interviews according to relevant points made by the interviewees, following the principles of content analysis [30]. As registered on the informed consent form they signed, all interviewees agreed with the recording of the conversation, although only some agreed to disclose their institutional affiliation in our published work; therefore, in this paper the affiliation of some interviewees is not specified.

Second, primary regulatory documents and guidance relevant to ATMPs were analyzed. We used the same codes of the content analysis (as explained above) so it was possible to identify common themes between interviews and regulatory texts. This included documents such as Regulation EC no 1394/2007 of the European Union (known as the ATMP Regulation) [31], the UK Specials scheme (MHRA Guidance Note 14, 2014) [32] and the MHRA's new regulatory framework proposal for POC manufacture [33].

Third, some quantitative data were retrieved, with the aim of giving an idea about the occurrence and distribution of activities related to, associated with, and necessary for ATMP POC manufacture. We had recourse to data made available on the websites of the Medicines and Healthcare products Regulatory Agency (MHRA) [34], the Human Tissue Authority (HTA) [35], and the UK Accreditation Service. For data processing and the production of maps, the R programming environment [36] was used, namely the following libraries: dplyr, readr, stringr, PostcodesioR, pdftools, sp, rgdal and ggplot2.

The following analysis reveals the challenges of ATMP production, shedding light on issues important for the determination of POC manufacturing readiness, focusing on the example of the UK and its national health service (NHS).

The current landscape of ATMP manufacture in UK hospitals

As explained above, the UK has the Specials manufacture regulatory scheme for the oversight of small-scale, bespoke therapy production in hospitals. The scheme can be used for a variety of therapies, including those that can be classified as ATMPs. For example, the Specials scheme is being used for the manufacture of a product combining cell and tissue engineering techniques, which is aimed at fighting an eye condition called limbal stem cell deficiency. The therapy, which began to be clinically used in 2019, has been developed at Newcastle University [37].

Nevertheless, the Specials scheme has limitations when it comes to producing therapies at large scale, in many hospitals. For example, it creates heavy burdens in terms of adding hospitals to, or dropping hospitals from, the list of manufacturing sties. As a consequence, the MHRA is now proposing a new regulatory framework, which has been specifically designed for POC manufacture and was submitted to public consultation in 2021 [33]. This framework is one of the initial outcomes of the regulatory powers gained by the MHRA after the UK's separation from the EU (so-called 'Brexit'). It applies to a broad range of therapies, including ATMPs, and is expected to be approved into law in 2022. It is decisively based on the concept of control site, an institution (probably a biotech or pharma company) that will design and implement the manufacturing system, recruiting hospitals, providing equipment and training, and eventually securing marketing authorization for the product [12,13].

Even though the MHRA regulatory framework proposal does not provide an official definition for POC manufacture, analysis of the public consultation document reveals a two-step approach. Initially, it is explained that the framework covers products "*manufactured at the point where a patient receives care, [for example] personalized medicines made for the patient either within or very close to the healthcare setting*"; subsequently, it is said that those products "*will need to be manufactured at a large number of sites*" [33]. Compared with the regulatory schemes currently in use for therapy manufacture in hospitals, the emerging UK scheme then brings about some novelties, as illustrated in Table 2.

Table 2. Regulatory schemes for therapy production at point of care.

Feature	Ongoing schemes		Emerging scheme
	Hospital exemption (EU)	Specials manufacture (UK)	Point-of-care manufacture (UK)
1. Is the license used by hospital clinicians?	Yes	Yes	Probably not
2. May the license be granted to a company?	Yes	Yes	Yes
3. May some hospital infrastructure be used in therapy manufacture?	Yes	Yes	Yes
4. May some hospital staff participate in therapy manufacture?	Yes	Yes	Yes
5. May therapy production happen outside the hospital?	Yes	Yes	No
6. Does the license cover manufacture in several hospitals?	No	No	Yes

Any given therapy, in any disease area, might in principle be produced under any of these three regulatory frameworks. What will determine the choice of regulatory scheme is, in addition to the location of the manufacturer, the attributes of the medicine (e.g., its shelf life), as well as the technical and economic characteristics of the manufacturing system. For Hospital Exemptions and the Specials scheme, the therapy may be manufactured outside the hospital (feature 5, Table 2), which is generally done by granting a license to a company responsible for producing the medicine in its manufacturing unit for the hospital. In the framework being proposed in the UK, products will typically have a short shelf life, and manufacture will therefore always happen in the hospital. Furthermore, the new regulatory framework will, in theory, no longer focus on the small-scale, bespoke manufacture governed by previous schemes but will address manufacturing systems involving large numbers of hospitals (Feature 6, Table 2). In this way, the last two features in Table 2 might suggest an upheaval in POC manufacture.

Indeed, it has been claimed that POC manufacture, as anticipated by the MHRA, will require considerable changes in hospital activities and much effort from hospital staff. Such awareness was manifested, for example, by interviewee 26 (MHRA) who declared that POC manufacture "*doesn't fit the current model of more tablets on a shelf, or more vaccines in the fridge* [. . .] *So, it will take time for them* [hospitals] . . . *it's not an incremental change. It's a disruptive change.*" In the domain of ATMPs more specifically, these challenges may seem to be even more substantial. As explained by interviewee 20 (King's College Hospital), hospitals working on ATMPs must establish various processes, including "*appropriate controls in place, document review, document creation, training at certain times. . . It's a lot of work.*"

The adaptations required by the UK's emerging regulatory framework are surely not negligible. However, in the specific field of ATMPs, two circumstances can soften the disruptions brought about by the emerging framework. On the one hand, ATMPs frequently target rare conditions with small patient populations. In this way, at an initial moment, hospitals manufacturing ATMPs are not likely to be in the large numbers announced by the MHRA; rather, a few hospitals may become manufacturing hubs, receiving patients from large geographic areas. On the other hand, hospital staff will not be starting all the necessary work from scratch. Thanks to previous small-scale therapy manufacture that has been conducted in hospitals (via the Specials scheme), some infrastructure has been installed, and some technical, informational and regulatory expertise developed, which will become useful when the emerging regulatory framework has been approved and used.

In January 2021 we consulted the MHRA's Register of Licensed Manufacturing Sites [34], which contains information on institutions licensed under the Specials scheme. Selecting only therapy groups within or around the domain of ATMPs, we obtained the results shown in Figure 1.

Figure 1 provides us with an interesting picture, showing, for example, that over 50 hospitals are authorized by the MHRA to produce tissue-engineered products.

As explained above, the Specials scheme applies to small-scale production, which is different from the logic fostered by the MHRA's new regulatory framework on POC manufacture, where the agency expects to see larger manufacturing scales, more automation, and the involvement of much larger numbers of hospitals, clinicians and patients. However, the current small-scale ATMP manufacturing activities have made it possible to put in place skills and resources which can surely prove useful when POC manufacture becomes more widespread and routinized. For example, the Specials scheme (like the EU's Hospital Exemption) requires that GMPs be complied with, leading to the adoption of procedures for materials testing, equipment certification, traceability and pharmacovigilance. It is in

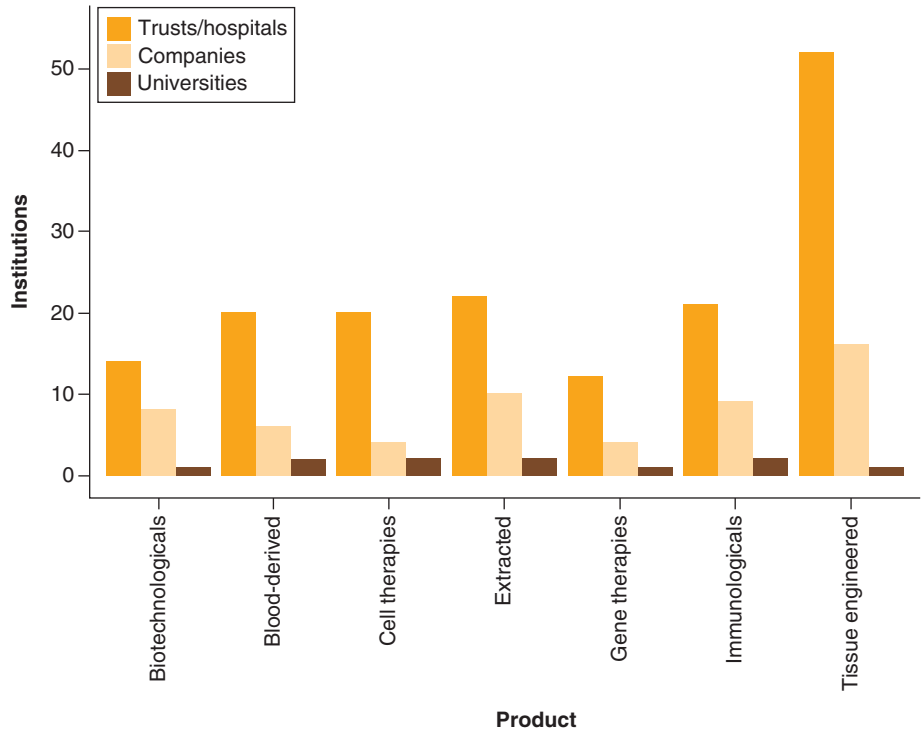

Figure 1. Institutions licensed to manufacture 'Specials' according to type of product, January 2021.

this sense that we point to a gradual, and frequently unnoticed, enhancement of the POC manufacturing readiness of the hospital landscape. If necessary, some hospitals will be able to provide experienced staff (e.g., clinicians, pharmacists or laboratory technicians), appropriate space, and certified equipment for more robust manufacturing systems, including those which may be led by commercial manufacturers.

However, a limitation of the data in Figure 1 has to be pointed out. It is known that these hospitals are authorized to manufacture, but there is no information available on whether they are actually doing so. In this way, considering that Specials licenses are today the 'mainstream regulatory solution' for UK clinicians producing ATMPs, these data can be framed as a good proxy but not as conclusive information.

The difficulties and adaptations required by POC manufacture relate not only to the work conducted in hospitals but also to the tasks of regulators. Even though the latter have framed the production of therapies in hospitals as an exceptional case, they have overseen its procedures by having recourse to traditional tools such as licenses for institutional accreditation. For example, the HTA, which regulates the use of organs, tissues and cells in the UK, requires that institutions willing to procure, store and process biological materials, such as the ones necessary for ATMP manufacture, obtain a license. Hospitals are among the main institutions holding such HTA licenses, as seen in Figure 2 (prepared with data collected in January 2022 from the website of the HTA) [35].

It is not surprising that hospitals are the main players in all the activities listed in Figure 2 (apart from importation), because clinical staff very frequently collect patient samples, such as blood and tissues, to perform examinations; hence the dominance of hospitals in procurement activities, with over 100 hospitals licensed for such tasks.

As explained by interviewees 20 and 21 (King's College Hospital), the HTA license is given to a hospital department and covers certain activities, as specified in the license document; when license holders wish to add other activities, they can extend the original license instead of having to apply for a completely new one. Even though HTA licenses do not cover manufacture (which is in the remit of the MHRA), the activities overseen by the agency are a prerequisite for manufacture. Indeed, manufacturing a therapy out of a patient's cells would be at odds with regulations if those cells are not properly procured, tested for quality, and stored in line with the HTA's requirements. In this way, the licenses shown in Figure 2 constitute a sort of regulatory pillar that might support manufacturing activities in the future. To a large degree, in the current situation, POC manufacturing readiness

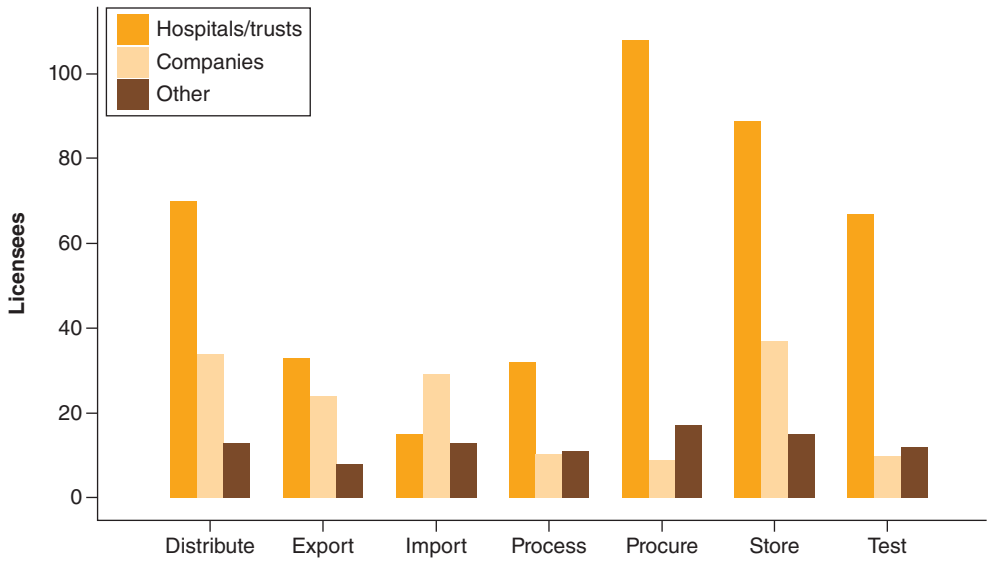

Figure 2. Institutions holding Human Tissue Authority licenses to work on biological materials, January 2022.

emerges in such indirect ways; that is, it derives from structures and licenses that have not been specifically obtained for manufacturing activities.

HTA licenses are also necessary for the conduct of clinical trials in hospitals. In this case, the candidate therapy is sometimes manufactured at point of care. Thus clinical trials, and particularly international research protocols, have contributed to the installation of expertise and infrastructure that also prepare hospitals for therapy manufacture. In this regard, the UK is well positioned, being one of the main world hubs for clinical experimentation [28].

At the moment, it is not straightforward to find accurate data for a study on POC manufacturing readiness, because hospitals' current therapy production activities have been carried out sporadically, without consistent collection of information. To address these difficulties, this section has attempted to present some data that can serve as proxies for current activities in ATMP manufacture in UK hospitals. Further data, along with information from qualitative interviews, are presented in the next section, with the aim to further understand how POC manufacturing readiness emerges, and to analyze three of its key components.

Results: key components of POC manufacturing readiness in ATMPs

POC manufacturing readiness is a multifactorial phenomenon, in the sense that several resources, skills and institutional processes must be present for it to be realized. In this section we outline three of its fundamental components: staff, infrastructure and external relations.

Staff & institutional procedures

ATMP POC manufacture demands the presence of a set of skills. Considering cell therapies, for example:

> "*the cell manufacturing process is labor intensive, as it comprises many* [. . .] *handling steps (e.g., density gradient cell processing, gene modification, washing, feeding and so on) that require interventions from committed skilled operators who have undergone extensive training*" [25].

To cover some of these necessary procedures, checklists have been prepared by the Advanced Therapy Treatment Centres, a network that aims to speed up the development and delivery of ATMPs [38]. These documents deal with several aspects pertaining to working with ATMPs in hospitals, such as cell handling, transportation of materials, and cryopreservation, in addition to addressing issues of risk assessment [9], auditing and organizational changes [9,38].

As the adverse effects of ATMPs can be severe, it is critical that their quality be strictly monitored, hence the central role played by a so-called qualified person (QP): the professional indicated on the manufacturer's license as being legally responsible for making sure that the product has been manufactured in line with parameters of quality and efficacy. Approval from a QP is required on completion of manufacture for any product. This is particularly demanding in the case of ATMPs, and especially in personalized products "*where the manufacture of one batch*

provides treatment to only one patient [. . .] *As such the manufacture of ATMPs creates an unprecedented demand for QP resource*" [39].

In the UK, those willing to become QPs need to acquire experience with the manufacture of medicines, undergo specific training, and be interviewed in one of the three institutions capable of certifying QPs: the Royal Society of Biology, the Royal Society of Chemistry or the Royal Pharmaceutical Society. The latter is generally where most hospital-based QPs are accredited, but it does not publish its list of registered QPs. By consulting the Royal Pharmaceutical Society directly, we learned that since 2011, 66 QPs have been accredited, 17 of whom are based in hospitals. It is then possible to compare these figures with published registers. Of the 147 QPs registered by the Royal Society of Chemistry since 2011, only three are based in hospitals; and of the 16 accredited by the Royal Society of Biology, one is in a hospital. Adding up the three accrediting institutions, 21 hospital-based QPs have been registered since 2011. The other QPs are overwhelmingly based in companies.

Our interviewees generally claimed that the UK has an insufficient number of QPs, especially in hospitals. This constitutes a weakness from the viewpoint of POC manufacturing readiness, as therapy batches produced in hospitals will have to be approved before being delivered to patients. Furthermore, the training that has been offered to those professionals still follows the traditional logistics of therapy production. This point was made by interviewee 4 who is based in Biotherapy Services, a company that uses the Specials scheme to manufacture a wound-care product in a few hospitals. This therapy, whose starting material is the patient's blood, has to be produced at bedside, as the manufacturer has 15 seconds to apply it after manufacture has been completed. According to this interviewee:

> "*QP certification is all built around long stability, large batches, not the kind of niche end we are. So, we're stuck doing a paperwork exercise in QP certification, which has zero value to patient safety, but we've got to do it to jump through the legal points.*"

In order to avoid unnecessary QP work, especially for the quick manufacture and delivery that may be necessary for some ATMPs, new ways to realize QP manufacture approval are being sought. Interviewee 4 explained that one idea is to provide QPs with a capacity they currently lack: delegating product release to a 'QP officer':

> "*the QP is releasing manufacture, so they're precertifying the product before it's made, on the condition that the final release elements are OK, and then the releasing officer is releasing the product provided they're OK* [. . .] *So, it's kind of precertifying the product conditional on a few simple things happening, which is then delegated to a releasing officer.*"

Interviewee 25 (MHRA) explained that the agency is also considering the possibility of authorizing off-site QP release. In this system, data pertaining to manufacture would be sent from the manufacturing site (the hospital) to the QP, who, from a different site, would approve (or not) product release based on such data.

If the issue of QPs is far from being solved, hospitals have advanced in other staff aspects that enhance POC manufacturing readiness. Some have created so-called ATMP committees. According to interviewee 27 (an ATMP pharmacist), the creation of such committees is not mandatory but has been recommended by the Pan-UK Pharmacy Working Group for ATMPs, formed by pharmacists from different British hospitals (www.sps.nhs.uk/networks/pan-uk-pharmacy-working-group-for-atmps/). This interviewee claimed that the list of institutions holding an ATMP committee includes the Newcastle Hospitals NHS Foundation Trust, University Hospitals Bristol NHS Foundation Trust, and Manchester University NHS Foundation Trust. Another example is King's College Hospital, where interviewee 20 is based. This professional gave the following explanation:

> "*The ATMP oversight committee is responsible for ensuring that any ATMPs that are coming through the hospital are being used appropriately, that* [. . .] *everybody who needs to know knows about the ATMP product, and that they are* [. . .] *being used in the hospital in a way that is safe and effective.*"

When an ATMP is processed in a hospital, various departments and facilities – such as testing laboratories, pharmacies and clinical wards – are frequently involved, and ATMP committees can play a liaising role. This same interviewee explained that after its review, the committee mobilizes different areas of the hospital, so they can reserve physical space, update documentation and perform other necessary tasks. When ATMP POC manufacture becomes more frequent, these ATMP committees will play a decisive role, either by having their responsibilities expanded or by serving as a model for the creation of even more specialized committees in hospitals.

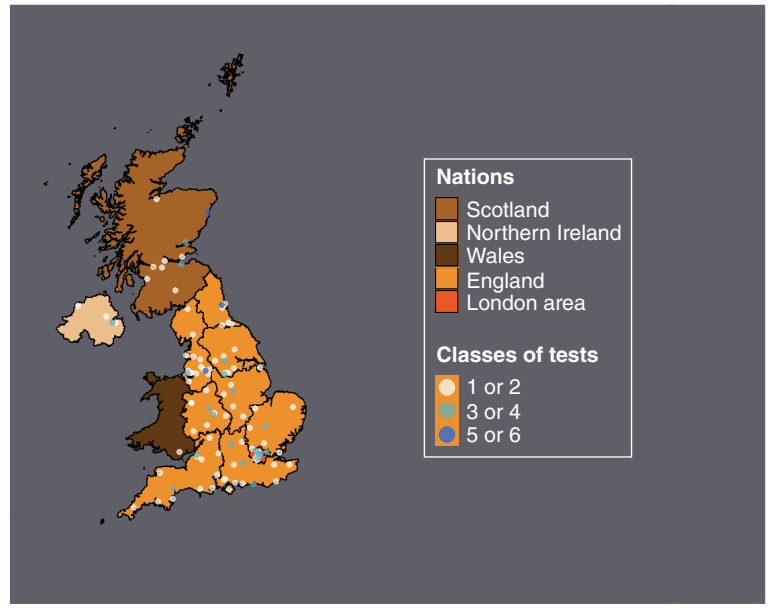

Figure 3. Hospitals and trusts with medical laboratories certified to ISO 15189, March 2022.

The presence of QPs and ATMP committees enhances POC manufacture, but more hospitals and trusts still need to become aware of such trends. As claimed by Pearce *et al.* [8], professionals based in hospitals, especially those who combine clinical and academic tasks, frequently neglect the issue of 'manpower resources', especially when they have "no history of cell therapy manufacture". However, staff and work organization are not the only issues to be considered, as we will see below.

Physical space & equipment

As noted before [14], "*The manufacture of cell and gene therapies will undoubtedly incur high costs for changes to infrastructure, requiring significant investment.*" These changes and investments can be even more substantial for hospitals, as they were not originally designed to host manufacturing activities, thus urging today's hospital staff to find ways to accommodate manufacturing activities in the clinical setting. Interviewee 25 (MHRA) imagined some solutions that might emerge, stressing that the regulatory agency is prepared to adjust to different solutions:

> "*supposing a hospital has 12 operating theatres, you're going to have a room next to each operating theatre, or in a central location. So, we're not being prescriptive here. If it needs it, and it needs some equipment that can't be moved, and the product has a reasonable shelf life, say 30 minutes or an hour, or something – yeah, fine.*"

In addition to space and manufacture itself, it is important to consider a range of supporting activities. Elsewhere we showed, for example, that POC manufacture will necessarily involve a growing use of software and informational infrastructure [67].

Another key role is likely to be played by hospital laboratories, which may be mobilized for performing tests on tissues and cells as part of the quality control associated with therapy manufacture. In the UK, as in several other countries, these laboratories have updated their procedures by seeking accreditation in line with international standards [40,41]. Particularly popular among hospitals has been ISO 15189, "*a specialized set of requirements developed to provide a standardized quality management framework which takes into account the specific nature of the work undertaken in a medical laboratory setting*" [41].

In March 2022 we consulted the website of the UK Accreditation Service (www.ukas.com/) and searched for hospitals holding the ISO 15189 accreditation for their medical laboratories. We found 107 hospitals or trusts, as shown in Figure 3.

Figure 3 shows that the 107 accredited laboratories are spread across the British territory, even though a better coverage can still be sought in Wales. For this map, we considered six categories of laboratory tests generally performed for quality control of ATMPs: cytogenetics, cytology, histocompatibility/immunogenetics, immunology, microbiology, and molecular genetics. Most hospitals (83) are accredited for one or two classes of tests, microbiology

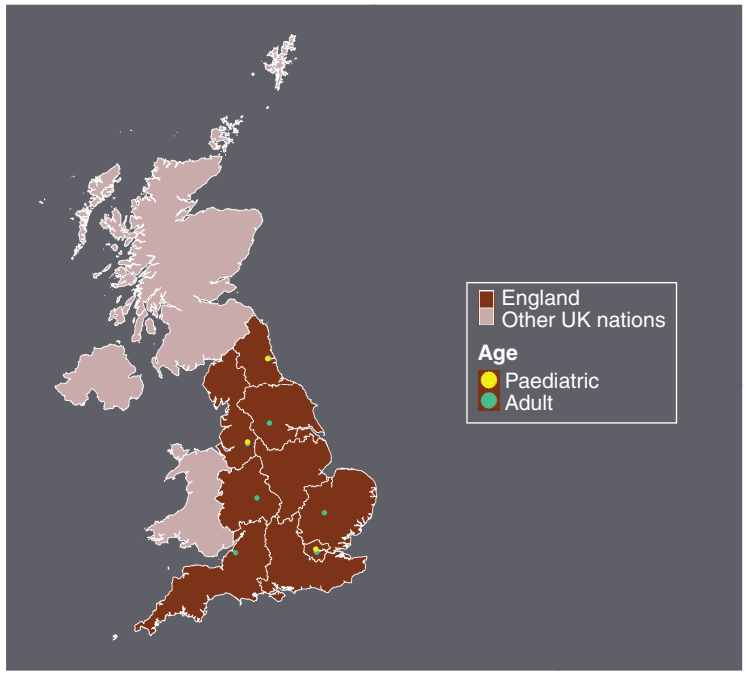

Figure 4. Location of the hospitals delivering Chimeric Antigen Receptor T-cell therapies in England, March 2022.

being the most usual one; 21 hospitals are accredited for three or four classes; and three are accredited for five or six classes.

The value of adopting the ISO 15189 standards has been the object of some controversy. Some authors claim that these standards improve the laboratory's quality and efficiency [42], whereas others argue that certification is only advantageous in the initial years of implementation [41]. In addition, some authors have voiced harsh criticisms against the use of ISO standards in hospitals [43,44], claiming that "*accreditation leads to substantial misdirected effort and waste*" [44]. Whether accreditation yields clinically beneficial outcomes or not, the widespread accreditation to ISO 15189 shown in Figure 3 makes it easier for hospitals to join international clinical trials while complying with the procedures familiar to the trials industry. It also indirectly enhances POC manufacturing readiness, as it creates quality control expertise that may support manufacturing activities.

Another medical facility that may play an important role in ATMP POC manufacture is the stem-cell laboratory. This is the facility that analyses, processes and stores cells deriving from bone marrow or blood collected for transplant. The relevance of these laboratories has become clear in the domain of commercial Chimeric Antigen Receptor T-cell (CAR-T) products, which derive from gene editing techniques and are designed to fight resistant cancers. NHS England, by adopting the standards of the accreditation committee of the European Society for Blood and Marrow Transplantation [45], has made it mandatory that the 12 hospitals delivering this kind of ATMP have a stem-cell laboratory for testing the starting material (white cells derived from blood) and storing the final product received from the manufacturing company. The location of these hospitals is shown in Figure 4.

Some of these hospitals are delivering CAR-T therapies for children, while others are doing so for adults. According to interviewee 29 (NHS England), this CAR-T network will receive new hospitals in the course of 2022. Even though commercial CAR-T therapies are produced in very centralized ways (as it is possible to freeze both starting materials and final products), the maintenance and expansion of the English CAR-T network indirectly enhances POC manufacturing readiness in the country. Considering that blood or blood cells will likely be the starting material for other types of ATMPs, all those stem-cell laboratories are in fact gaining an expertise that may be key for POC manufacture in the future.

Not to be neglected is also the need for equipment, which will be necessary for at least three purposes. First, there is the obvious need for manufacturing equipment, bearing in mind that ATMPs will ideally be produced in so-called closed systems where starting materials and reagents are processed within machines, with little human manipulation, so the risk of contamination and human errors is reduced [46]. Second, in ATMPs it is sometimes possible to freeze starting materials and final products, which requires equipment for accurate temperature control so that living structures are not damaged [47]. Finally, considering that some ATMPs will consist of a combination

Table 3. Medical institutions with GMP manufacturing facilities, 2021.

Institution	City	Product	Manufacture and/or import medicinal products?	Manufacture and/or import medicinal products for clinical trials?
Great Ormond Street Hospital	London	B	Yes	Yes
Guy's Hospital	London	B	No	Yes
Hammersmith Hospital	London	C	No	Yes
King's College Hospital	London	C	No	Yes
Royal Free Hospital	London	C	No	Yes
Queen Victoria Hospital	East Grinstead	C	No	Yes
Scottish Centre for Regenerative Medicine	Edinburgh	C	Yes	Yes
The Newcastle Hospitals NHS Foundation Trust	Newcastle	B	No	Yes

B: Both cell and gene therapies; C: Cell therapies.
Table prepared using data from [49].

of applicator and cells [48], it is possible to imagine situations where the applicator can amount to a device requiring some space in the operating room or at bedside.

These considerations might suggest that POC manufacture requires the installation of actual manufacturing units within hospitals. According to the ATMP Regulation of the EU (Regulation 1394/2007), still valid in the UK, ATMPs must be produced in line with GMP [24]. Some British medical institutions have installed GMP manufacturing facilities, as seen in Table 3 (prepared with data from a recently published report) [49]:

These eight facilities are authorized to manufacture for clinical trials, but only two can manufacture products for clinical use. These are, today, the only two hospital-based units that could produce ATMPs at relatively large scale. Depending on strategic decisions, this number might grow, with more GMP facilities being installed in other hospitals. However, previous analyses have pointed out the complexities and high costs associated with building up a GMP facility in a hospital [15,50]. As interviewee 15 (University College London) put it: "*the challenge with a GMP manufacturing suite, especially if it's run by the hospital, is how you cover the costs to make it sustainable, because it's very expensive to run a GMP facility.*"

Furthermore, installation of a manufacturing facility entails much regulatory work. Interviewee 31, based in one of the institutions in Table 3 (Royal Free NHS Trust), explained that the hospital's manufacturing facility is inspected by the MHRA every 2 years: "*we have to do things like installation qualification, operational qualification and* [. . .] *performance qualification for all equipment. Those are the kinds of guidelines that* [. . .] *the MHRA would be looking for in an inspection.*"

This is not to say that equipment has no relevance when manufacture happens at small scale, like in the framework of the Specials scheme. Even in this case, some equipment is still needed for quality control. As explained by interviewee 20 (King's College Hospital), flow cytometers, water analyzers, and devices for bacterial sterility tests are examples of equipment necessary for these purposes. Therefore, POC manufacturing readiness is not enhanced only via large-scale production. Furthermore, the MHRA's new regulatory framework will not abolish the old Specials scheme, which guarantees the continuation of small-scale, bespoke manufacturing activities in hospitals.

The use of equipment points to parallel issues: the need for reagents and the connections between hospitals and external providers. These are analyzed in the following subsection.

Relations with providers & distributors

In order to perform POC manufacture (at both small and large scale), hospitals need to engage in a series of external relations that we described as 'interfaces' in a previous publication [67]. Interviewee 20 (King's College Hospital) explained that the quality control activities carried out in the hospital involve several products, some of which may be imported:

> "*For the quality control and the collection* [of samples] *and processing, there's a lot of consumables and reagents. We require reagents for the flow cytometer, for the water analyzer, collection kits for the apheresis, and other various consumables associated with that, sample tubes* [. . .] *and any other disposable consumables for all the processing [. . .]*"

Thus the production of a therapy in a hospital entails the procurement of a quite long list of products, be it for collection of starting materials, quality control or manufacture itself. For example, Smethurst *et al*. manufactured red blood cells at the Component Development Laboratory, which is part of NHS Blood and Transplant [51]. This production, aimed at supporting a clinical trial with cardiac surgery patients, required the use of 32 reagents provided by nine companies, only three of which are located in the UK.

Another major challenge of ATMP manufacture is that starting materials and final products cannot be transported easily due to the presence of fragile living structures such as cells [52,53]. "*During this transporting period, preservation of cell viability* [. . .] *is extremely important because the clinical effect can vary depending on the cell quality*" [54], hence the need to control factors such as temperature and vibration if it becomes necessary to transport cells and tissues [48].

Currently, hospitals procuring or shipping biological materials are using commercial courier services [55]. These companies "*have designed specialized package tracking and monitoring programs developed specifically for healthcare and scientific businesses*" which have been used by hospitals as well. Interviewee 34, based in eCourier, a company offering transportation services to hospitals, explained that the company has secured the ISO 9001 and the ISO 14001 certifications, in addition to seeking the ISO 27001 certification:

> "*They are not mandatory but if we don't have this, then* [. . .] *we wouldn't be able to go for the NHS-type contracts, because that's an expectation, usually, of the NHS* [. . .] *So in their tenders, they'll put there 'ISO 9001'* [. . .] *it's a mandatory field, and you have to say yes or no. If you tick 'no', then you'll get marked down.*"

This use of ISO certifications is a way in which hospitals have tried to ensure quality in their relations with companies transporting materials and samples. However, it is not known whether current approaches will continue to work for cells yet to be explored and ATMPs yet to be developed, "*especially with regard to functional outcomes in vivo*" [52]. Due to such uncertainties, a range of studies have been published to understand the implications of commercial transportation for cells and tissues [10], to test the outcomes of different transport conditions [54] or to develop completely new transportation containers or protocols [56,57].

Finally, POC manufacture, at least in the models envisaged by the MHRA, will probably be organized as a relationship between the hospital and an external service provider. Hospitals will probably be visited by companies offering POC manufacturing services. As explained above, Biotherapy Services is the company currently carrying out such activities, with a product manufactured with a Specials license. However, the Specials scheme has not been sufficiently flexible for the company, as it is not very easy to add hospitals to, or remove hospitals from, the license. Moreover, the ways in which QP approval of batches is performed seems detrimental to the expedient procedures necessary for this bedside manufacture. It is expected that the MHRA's new regulatory framework will solve these difficulties.

As a result, companies can become frequent 'guests' in clinical settings, as claimed by interviewee 27 (ATMP pharmacist): "*we need a similar set-up (with guidance and things that we put in place for ATMPs) for POC manufacturing, because that will involve companies coming in, I suspect.*" Therefore, considering current trends, POC manufacturing readiness will involve hospitals' capacity not only to 'reach out' to external providers but also to negotiate conditions with mobile manufacturers and 'let them in'.

Understanding these technical trends is then fundamental for enhancing POC manufacturing readiness. Furthermore, it is also key to pay attention to other institutional issues also illuminated by this proposed concept, as discussed in the following section.

Discussion: POC manufacturing readiness & its implications

As pointed out from the outset, the concept of POC manufacturing readiness is not aimed at underpinning quantitative analysis, even though it can do so in the future when British institutions more consistently make available, directly or indirectly, data related to ATMP production in hospitals. In the current situation, the concept aims to shed light on regulatory, technical and institutional factors that have indirectly contributed toward building up POC manufacture. As the analysis above suggests, the UK is well positioned in this scenario, hosting expertise and infrastructure generated via previous experiences with the Specials scheme, as well as some production at GMP-compliant facilities which are now operating, for the most part, for clinical trials.

Nevertheless, it is important not to neglect the drawbacks and pitfalls that have been revealed in the course of our study. For example, we have shown that hospitals and some external providers have increasingly used some ISO standards to ensure quality and safety. Several recent studies have questioned the worth of such standards in

the case of hospital laboratories [41–44], claiming that such certification leads to "*substantial misdirected effort and waste*" [44] and the collection of "*over-bureaucratic documentation*" [43] without improving the services offered to patients. Therefore, a balanced approach seems to be useful here. On the one hand, one should not diminish the importance of standards for quality control and assurance; on the other, regulators should be prepared to intervene by publishing guidance, so that hospitals do not end up being overburdened with a plethora of standards that future POC manufacturing companies decide to adopt.

By the same token, it is important to ask to what extent new models of POC manufacture should imply strict compliance with market rationales. Many interviewees expressed a belief that several challenges will be tackled through market solutions. Interviewee 26 (MHRA), for example, was asked which players are likely to use the emerging regulatory framework on POC manufacture:

> "*I think it will be difficult at the hospital end to do that. They will more than likely create a spin out. Big pharma I think is very wedded to the centralized model of manufacture* [. . .] *I think some of them will definitely look at this as an opportunity for sure, but I would guess, in general, if you like, the early adopters* [. . .] *will be the* [small and medium-sized enterprise]*-type organizations.*"

As the emerging regulatory framework covers a large range of products, it is indeed reasonable to assume that hospitals will create spin-out companies for some types of POC manufacture. However, considering the specific characteristics of ATMPs, the association between manufacture and commercial exploration does not have to be automatic. In some cases, ATMPs focus on such small patient populations that companies tend to simply neglect the disease area [17].

In this regard, the flexibilities of the ATMP domain become very telling. On the one hand, GMP facilities must not always be very large and sophisticated. "*Small to mid-size facilities with three to ten cleanrooms may be a better strategic investment compared with large facilities*" [50]. On the other hand, the transportation of cells, tissues and final products can occur in different ways, as, for example, "*the same cell type might require a different shipping protocol, depending on the cell differentiation stage*" [53]. Therefore, imagining an economically and institutionally rigid ATMP manufacturing model, where only companies would be able to raise the levels of POC manufacturing readiness, as most players currently tend to do in the UK, amounts to neglecting some key features and potentialities of ATMP POC manufacture.

'Specials' manufacturing activities are possible only if therapies fight diseases that are not covered by products available on the market. Thus, some of the current Specials production may at some point be terminated when products have received a marketing authorization through the new POC regulatory framework. Perhaps anticipating future public controversies, some accusations have already been voiced against the Specials scheme: "*Critics have argued that, because their use is not governed by the formal rigor of a clinical trial, this provides a carte blanche for physicians to treat patients with untested products that may be potentially harmful or have only limited success*" [23]. Equally, in the EU, Hospital Exemptions are being questioned, with players arguing that "*it is important to ensure that* [. . .] *hospital exemption is not misused to circumvent the applicable legal instruments for the marketing of safe and effective medicinal products in Europe*" [58]. Therefore issues of POC manufacturing readiness will also involve the strategic ways in which such readiness is used, with implications for public policies and healthcare expenditure.

In previous studies it has been claimed that the production of ATMPs at point of care implies lower costs for the hospital in comparison with the acquisition of such products from industry [15,59–62]. At first sight, then, therapy manufacture in hospitals promises to bring about some financial relief to hospitals and not-for-profit organizations willing to be involved in therapy production. However, the financial performance of those manufacturing systems will depend on a number of factors. If GMP manufacturing units are used, costs will only be saved in the medium-to-long term, because of the large investments required for setting up such units [15] in hospitals that may be under financial strain. Alternatively, if the system becomes heavily based on the operations of companies offering POC manufacturing services, therapies will arguably be priced based on the criteria currently used, such as the concept of Quality-Adjusted Life-Years (QALYs), which considers how long the patient lives after therapy administration, in the light of a quantitative indicator aimed to measure quality of life in each of these remaining years. This concept has become widely adopted, especially in oncology [63], and has underpinned the determination of very high prices. Finally, as we explained elsewhere [12,13], companies may be reluctant to fully explore POC manufacture if the hospital receives a substantial portion of healthcare reimbursement.

Another issue to be considered is that POC manufacture may trigger delicate dependencies. For example, it was seen above that manufacturing equipment is a major component of POC manufacturing readiness. As there are

Table 4. Annex: information on interviewees.

Number	Date of interview	Class (in Table 1)	Institution	Country where the interviewee works
1	November 2021	Regulatory agency	Not disclosed	Spain
2	November 2021	Company	Association of Pharmaceutical Specials Manufacturers	UK
3	July 2021	Hospital staff	Clinic Hospital Barcelona	Spain
4	June 2021	Company	Biotherapy Services	UK
5	June 2021	GMP manufacturing facility	University of Birmingham	UK
6	October 2021	Hospital staff	The Christie NHS Foundation Trust	UK
7	October 2021	Hospital staff	The Christie NHS Foundation Trust	UK
8	June 2021	Academic researcher	Cancer Research UK	UK
9	June 2021	Regulatory adviser	Joint Accreditation Committee of the International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation	Spain
10	June 2021	Regulatory adviser	Joint Accreditation Committee of the International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation	UK
11	June 2021	GMP manufacturing facility	Cell and Gene Therapy Catapult	UK
12	July 2021	Academic researcher	National University of Ireland Galway	Ireland
13	June 2021	Academic researcher	University College London	UK
14	July 2021	Academic researcher	University College London	UK
15	September 2021	Academic researcher	University College London	UK
16	July 2021	Government institution	Innovate UK	UK
17	June 2021	Academic researcher	King's College London	UK
18	July 2021	Hospital staff	University Hospital Lausanne	Switzerland
19	November 2021	Regulatory adviser	Not disclosed	UK
20	September 2021	Hospital staff	King's College Hospital	UK
21	September 2021	Hospital staff	King's College Hospital	UK
22	July 2021	Company	Lonza	USA
23	July 2021	Company	Lonza	USA
24	August 2021	Academic researcher	Not disclosed	UK
25	June 2021	Regulator	Medicines and Healthcare Products Regulatory Agency	UK
26	June 2021	Regulator	Medicines and Healthcare Products Regulatory Agency	UK
27	July 2021	Hospital staff	Not disclosed	UK
28	August 2021	Hospital staff	NHS Blood and Transplant	UK
29	January 2022	Hospital staff	NHS England	UK
30	July 2021	Regulatory adviser	Not disclosed	UK
31	August 2021	Hospital staff	Royal Free Hospital NHS Foundation Trust	UK
32	July 2021	Hospital staff	Not disclosed	UK
33	September 2021	Academic researcher	University College London	UK
34	February 2021	Company	eCourier	UK

NHS: National Health Service.

only a few companies developing such equipment, the manufacturing activities taking place in hospitals may end up depending on a few sources of reagents. Interviewee 31 (Royal Free NHS Trust) explained, for instance, that one of the devices used in the hospital's manufacturing facility is Prodigy, produced by the German company Miltenyi Biotec:

> "*There are some reagents and some products that are very very specific, and for some of them we'll have one supplier, because things like. . . because we're using the Prodigy, obviously there are many many things that we have to buy directly from Miltenyi, because* [. . .] *they make the device and they make the materials that we need to use with their device.*"

These difficulties were also pointed out in a 2018 study by DiGiusto *et al.*, who detected "*the use of sole-source providers for devices, reagents and disposables*" and explained that "*throughout the past 20 years, sources for reagents, disposables and devices have changed or disappeared from the market*" [64]. In this way, POC manufacture of certain vital therapies may eventually rely on the supply power of just one provider, creating vulnerabilities, especially in the face of possible disturbances of global supply chains.

In this way, POC manufacturing readiness depends on several technical components, as argued in the previous section, but has also to do with strategic choices made by policymakers, as well as the market logics that may come to predominate in the production of ATMPs at point of care.

Conclusion

Traditionally, little attention has been paid to the possible production of therapies and medical devices at point of care, "*as hospitals are usually perceived only as end-users of the products*" [65], not as manufacturers. However, a new approach begins to be promoted by some key players such as the MHRA, the UK's regulator for medicines and medical devices. The emerging regulatory framework proposed by this agency, specifically designed for POC manufacture, is a strong signal of this awareness. Nevertheless, the proposal of a new regulatory framework does not necessarily mean the introduction of completely new rationales and ways of working. We have shown that the production of medicines in UK hospitals can capitalize on several institutional, technical, infrastructure, and staff capacities that have been gradually implemented, in a process that we have tried to characterize with the concept of 'POC manufacturing readiness'.

Over the last years, the idea of readiness has been mobilized to highlight "*both the intra- and extra-organizational dynamics that shape the ways in which innovative technologies are given meaning, adopted and implemented*" [66]. The concept of POC manufacturing readiness is also endowed with this large scope. Hence one could focus on readiness from different angles, stressing the readiness of a country or a health system (as in this paper) or the readiness of a region, a hospital or even a ward within a hospital. In all cases, it seems important to consider the components described above: institutional and staff issues; material infrastructure; and relations with external providers.

The UK is certainly well positioned for the intensification of ATMP POC manufacture, considering that its hospitals have: a long tradition in international clinical trials, including manufacture for these trials; certifications given by regulators such as the HTA and the MHRA; experience with international standards for laboratory tests; access to specific guidance such as the documents prepared by the Advanced Therapy Treatment Centres network; and long relationships with providers of products and services, including couriers specializing in transportation of biological materials. At the same time, however, some weaknesses can be identified, such as the small number of QPs certified to oversee ATMP manufacture. In addition, there is in the country a growing reliance on, and widespread belief in, solutions from the market, which might create frustrations and shortages at critical junctures of market evolution.

POC manufacture will require various sorts of adjustments and efforts from various players, including regulators, companies and hospital staff. Furthermore, it will be necessary to look for appropriate analytical and interpretive tools to assess the evolution of emerging manufacturing solutions, especially for domains still filled with uncertainties, such as ATMPs. The concept of POC manufacturing readiness can possibly be a helpful tool for the conduct of these most necessary analyses and interpretations.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Summary points

- Point-of-care (POC) manufacture (the production of therapies in hospitals) is necessary when the medicine has a short shelf life and needs to be delivered to the patient immediately.
- So far, this production has been overseen by means of regulatory exemptions such as the Hospital Exemption of the EU and the 'Specials' manufacture scheme of the UK, covering bespoke therapy manufacture at small scale.
- The UK regulator is proposing a new regulatory framework intended to facilitate the dissemination and routinization of POC manufacture. This has been seen as an upheaval to the work performed in hospitals.
- However, considerable expertise and infrastructure has already been amassed in some hospitals, namely those that have joined international clinical trials, as well as those with experience with the Specials manufacture.
- The concept of POC manufacturing readiness (proposed here) points to this accumulation of capacities, which will be key in the future when POC manufacture becomes more disseminated and routinized.
- Three aspects of POC manufacturing readiness are analyzed here: staff and institutional procedures; material infrastructure and equipment; and relations with providers and distributors.
- The UK is well positioned for the expansion of POC manufacture, even though some weaknesses can be identified, such as: the uncertain benefits of a growing reliance on standards; the shape to be taken by hospitals' relations with companies providing manufacturing services; and the possible disturbances of supply chains on which POC manufacture will rely.

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