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**ADVANCED THERAPIES, HOSPITAL EXEMPTIONS, AND MARKETING AUTHORIZATIONS:
THE UK'S EMERGING REGULATORY FRAMEWORK FOR POINT-OF-CARE MANUFACTURE**

ABSTRACT

Hospital-centred manufacture, which consists in producing therapies close to the patient, within a hospital or in a nearby unit, is becoming increasingly viable and necessary. There are at least two modalities of this kind of manufacture: in what we name *bedside manufacture*, therapy production relies on hospital infrastructure and facilities, products can have all sorts of shelf life, and a small number of hospitals is involved; in the emerging modality called *point-of-care manufacture*, there is great reliance on portable manufacturing devices taken to the hospital, products have short or very short shelf life, and a large number of hospitals may be involved.

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has proposed a new regulatory framework dedicated to point-of-care manufacture. A large range of products can be manufactured this way, including some Advanced Therapy Medicinal Products (ATMPs), which are medicines based on cells, genes or tissues.

Bedside manufacture has been traditionally overseen via regulatory exemptions. In the European Union (EU), the manufacture of ATMPs in hospitals or for hospitals has been covered by the "Hospital Exemption". In the UK, another exemption, known as the Specials scheme, has been used. Both exemptions are grounded on the specificities of hospitals and clinical needs.

The MHRA's current regulatory proposal introduces a new rationale in which point-of-care manufacture will be subject to a flexible and proportionate framework while following the regulatory pathway now valid for commercial products, including the conduct of clinical trials and

the issuance of marketing authorisations. This brings about a market route that will coexist with the clinical route of exemptions.

This article analyses the implications and uncertainties of the UK's possible move from regulatory exemptions (bedside manufacture) to marketing authorizations (point-of-care manufacture) for hospital-produced ATMPs. It also sheds light on strategic issues triggered by the MHRA's proposal.

Keywords: Advanced Therapy Medicinal Products (ATMPs); hospital exemptions; marketing authorizations; point-of-care manufacture; regulation; Specials manufacture

I. INTRODUCTION

Therapy manufacturers, which have traditionally carried out their production in a few manufacturing units, are slowly proposing new approaches where much larger numbers of manufacturing units are mobilised [1, 2]. Among these systems, there is *hospital-centred manufacture*, a model where therapies are produced in either hospitals or units adjacent to hospitals. This paper focuses on the UK's changing regulatory framework for this kind of production. We analyse this emerging model and ask: when new ways of manufacturing therapies are proposed, how quickly and effectively can regulators react to such changes, and what are the implications of those technical and regulatory shifts?

As we showed elsewhere [3-5], if there is little time available from completion of therapy manufacture to administration to the patient, hospital-centred production can be a viable option. Occasionally, it will be the only solution available, especially if it is not possible to freeze materials or products for transportation, as rapid manufacture and application at the hospital are required. This is likely to be the case for a range of products, including Advanced Therapy Medicinal Products (ATMPs), a group of cutting-edge therapies based on genes, tissues or cells [6]¹. In addition to enabling expedient therapy delivery [7, 8], hospital-centred production of ATMPs has been said to bring about benefits such as cost reductions [7, 9-11], acceleration of bench-to-bedside innovation [7], and mitigation of risks generated by market shortages [10].

¹ This definition of ATMPs has been proposed by the European regulator – the European Medicines Agency (EMA) – and continues to be valid in the UK even after the country's departure from the European Union (Brexit). Further information about the European ATMP Regulation is provided below.

In order to make our analysis more precise, as well as account for the regulatory changes taking place in the UK, a distinction will be made between two kinds of hospital-centred manufacture, as summarised in Table 1.

Table 2Table 1. Two modalities of hospital-centred manufacture

Characteristic	Hospital-centred manufacture	
	1. Bedside manufacture	2. Point-of-care manufacture
Product's shelf life	Long, medium, short or very short	Short or very short
Responsible organisation	A hospital-centred team or a company hired by this team	In most cases, a company
Location of manufacture	The hospital or the company's manufacturing facility	The hospital
Infrastructure used	The hospital's infrastructure or the company's facility	Portable devices taken to the hospital
Number of hospitals involved	Small	Large
Kinds of therapies manufactured	Any kind of therapy	Therapies requiring rapid manufacture and immediate application

In *bedside manufacture*, therapy production relies on manufacturing resources (facilities, devices, equipment) present in either the hospital or the unit of a company hired by the hospital. In *point-of-care* manufacture, the therapy is always produced in the hospital, by means of portable manufacturing devices taken to the hospital by a company. It is important to explain that, as our study has revealed, bedside manufacture has been practised for decades whereas point-of-care manufacture is an emerging modality, with only a handful of companies having manufacturing systems with some of its features². Furthermore, it is key to reiterate that point-of-care manufacture will be applied when products have short or very short shelf life, as freezing the product for transportation would compromise its stability or potency. This may be the case for different kinds of cells or tissues, as well as different disease areas. Ongoing and future research

² Below we will focus on the example of Biotherapy Services, a company that is currently manufacturing, at some NHS settings, a product of very short shelf live.

and development activities will therefore indicate what ATMPs will require this model of manufacture.

The difference between *bedside manufacture* and *point-of-care manufacture*, which we introduced above for analytical purposes, is not found in existing literature or regulatory texts. Even though many analysts would consider these phrases as synonymous, the distinction is important here, as it will make it possible to analyse various regulatory aspects of hospital-centred manufacture, as well as the shifts now taking place in the UK. Furthermore, the distinction reflects a usage that is gaining recognition in the UK and may therefore not be in line with the terminology adopted in other countries.

So far the assumption made by regulators in different countries is that in clinical settings, it may be difficult or impossible to follow all the strict regulatory procedures typically adopted by companies producing ATMPs [11]. When therapy manufacture occurs in hospital, the manufacturing staff, equipment, and material infrastructure are present primordially for clinical reasons, not industrial reasons. Moreover, the production may occur under clinical pressure that is never faced by the industry. Manufacturing therapies within or close to the hospital would then justify the application of exemptions from some regulatory requirements such as conduct of some tests and specifications for final products.

For these reasons, exemptions have been used in different jurisdictions for the regulation of hospital-centred therapy production. Different exemption schemes may even coexist in the same jurisdiction, like in the UK's case. The country has had a regulatory exemption scheme known as the "Specials scheme" [12-14]. In parallel, the UK recognises the Hospital Exemption scheme, which was created in 2007 by the European Union and was transposed into UK law by means of the 2010 "Guidance on the UK's arrangements under the Hospital Exemption scheme" [12]. The EU's and UK's exemptions are similar but the British one is more flexible, as it enables the importation of unlicensed therapies, the prescription of therapies by dentists and supplementary prescribers, and the administration of products outside hospitals. Thus the UK constitutes an interesting case in which two exemption schemes that can be used for hospital-centred manufacture coexisted for over ten years.

Technology advancements have heightened the viability of manufacturing ATMPs, including in hospital settings [7, 8, 15]. It is in this context that the UK has gained regulatory autonomy as a result of its departure from the EU (so-called Brexit), with the resulting Medicines and Medical Devices Act (MMDA 2021) [16], which provides the UK's Medicines and Healthcare products Regulatory Agency (MHRA) with authority to introduce or change regulations pertaining

to human medicines and medical devices. The MHRA has been aware of the potential expansion in hospital-centred manufacture, including the emergence of point-of-care manufacture. As a result, the agency is proposing a new regulatory framework specifically designed for point-of-care manufacture, which was submitted to public consultation from August to October 2021 [17]. If approved, the framework will apply to a broad range of therapies, which includes ATMPs but also products such as medical gases, blood-derived medicines, and 3D printed medical devices.

This proposal introduces, for point-of-care manufacture, a key change in relation to the ways in which bedside manufacture used to be regulated: point-of-care manufacture will take place, no longer in the framework of exemptions, but in the framework of marketing authorizations. In this way, it will be possible to manufacture therapies in hospitals while aiming for the conduct of clinical trials and, eventually, the issuance of a market authorisation. This represents a considerable shift, as hospital-centred manufacture has traditionally warranted bespoke and special regulatory requirements, with products being delivered without the need for marketing authorisations, and therefore not provided as commodities on the market.

In this way, the MHRA's regulatory framework opens up a rich opportunity for the study of the move from exemptions (bedside manufacture) to authorizations (point-of-care manufacture). This article aims to identify the emerging issues, uncertainties, and potentialities of this passage. What are the challenges and promises of the UK's emerging point-of-care regulatory framework for ATMP development and production? What sorts of technical and political trends does it reflect or facilitate?

To address these questions, this article is organized as follows. Initially, we introduce the research methods on which our study has been based. We move on to analyse the UK's landscape for bedside manufacture and its dual exemption approach (with the Specials scheme and the Hospital Exemption). Subsequently, we describe the MHRA's point-of-care regulatory proposal, analysing its rationales, potentialities, and challenges, with a focus on ATMP manufacture. The final section brings some closing considerations.

RESEARCH METHODS

This research project has been conducted at the Department of Science, Technology, Engineering and Public Policy of University College London (UCL) since 2017. Its main goal is to analyse the regulatory challenges in the manufacture of ATMPs. In addition to a literature review,

the project mobilises the following three methods, which have been reviewed by and approved by UCL Research Ethics Committee.

First, in-depth qualitative, semi-structured interviews have been conducted with professionals involved in the development or manufacture of ATMPs, including entrepreneurs and academics working towards enabling hospital-centred manufacture. The range of the interviewee's expertise is summarized in Table 2.

Table 2. Qualitative interviews: interviewee's affiliation*

Institution	Interviewees		
	In the UK	Other*	TOTAL
Pharma/biotech company or contract manufacturing organization	6	4	10
Hospital department	8	2	10
University research laboratory	6	3	9
Regulatory agency, regulatory consultancy firm or government agency	11	6	17
GMP manufacturing facility**	5	0	5
TOTAL	36	15	51

* Ireland, Germany, Spain, Switzerland, Belgium, Israel, and United States

** GMP manufacturing facilities are therapy production units funded by public bodies; contract manufacturing organizations are companies selling therapy manufacturing services to other companies

In line with our research ethics approval, interviewees were given the option whether to associate their interview with their institutional affiliation. Therefore, in this article, not all

interviewees have their institutional affiliation specified. All the interviews were recorded with informed consent from the interviewee.

The interviews explore the scientific, technical, institutional, and political challenges of ATMP development and manufacture, including the challenges entailed by hospital-centred manufacture. We also explored the interviewees' opinion about the UK's emerging regulatory framework for point-of-care manufacture.

For analysis, different parts of the interviews received codes based on the topics addressed by the interviewees (content analysis). In this way, it was possible to identify recurrent concerns, hopes, and uncertainties held by those who are somehow involved in, or aware of, ATMPs, their development and manufacture. The same codes were also used in the notes we have taken in our literature review, so we can relate what interviewees declared to other strands of our project. With this approach, relevant and recurrent themes emerge from our research data, in such a way that we are then able to connect themes in a coherent interpretation.

Second, a quantitative analysis of the UK Specials scheme was conducted. This was done with data published by the MHRA on its website [18]. Some charts, tables, and maps were thus produced, providing an overview of this regulatory scheme. For data processing and visualization, the R programming environment [19] was used³.

Finally, we hosted an online workshop that addressed the challenges of ATMP point-of-care manufacture, as well as the MHRA's regulatory proposal. The workshop took place in June 2021 and was joined by 32 specialists in the field of ATMPs, pharmaceuticals, therapy manufacture, and regulation. Prior to the event, all participants were informed that the workshop would also involve information collection for our research project. The discussions of the event were the object of a separate publication [5].

Based on these research methods, we present here an analysis of the rationales and trends introduced by the MHRA's point-of-care regulatory proposal. Initially, the following section outlines the ways in which regulatory exemptions have traditionally been used for hospital-centred therapy production.

³ More specifically the following libraries: dplyr, readr, stringr, PostcodesioR, pdftools, sp, rgdal, and ggplot2.

BEDSIDE MANUFACTURE: THE IMPORTANCE OF REGULATORY EXEMPTIONS

A. The international landscape

Regulatory exemptions have long been used, in many economic sectors, as they enable flexible and fine-tuned regulations [20]. They may receive different names: exceptions, waivers, variances or adjustments [21]. They are put in place whenever the regulator frees some people or entities from certain obligations or requirements. In other words, we are dealing with “[...] those exemptions granted by agencies exercising their inherent authority to make exceptions to general regulations” [21]. In spite of its frequent occurrence, this mechanism is not always studied in detail [21-24] and there is still much to be analysed about “the little-known nature of regulatory exemptions” [21].

Exemptions can be considered as necessary when certain activities are carried out in unusual locations. This is what happens when therapies are produced in hospitals instead of specialised manufacturing units. In the case of ATMPs, regulators have indeed been aware of the specificities of hospital-centred manufacture. In 2001, for example, the USA Food and Drugs Administration (FDA) created the “Same surgical procedure exception” [25], allowing the manufacture of human cells, tissues or cellular-centred products with no need for the mandatory registration, as long as the product is autologous (derived from biological samples of the patient to whom the therapy is destined) and collected, produced and implanted, in a single surgical procedure [26].

Another key example has been the “Hospital Exemption” created in the European Union (EU) [12, 27-32]. The scheme was introduced in article 28 (paragraphs 2 and 3) of the Regulation 1394/2007, the so-called ATMP Regulation [6], which came into force in 2008. This Regulation created the Hospital Exemption by supplementing the provisions for marketing authorisations under Directive 2001/83/EC. The supplementation also introduced the definition of ATMPs, products based on cells, genes, or tissues. When a medical device or implantable medical device is also present, this constitutes a combined ATMP. In this way, the European regulation states that these therapies should be considered as medicinal products (or “advanced” medicinal products) and should therefore be developed in accordance with the requirements valid for such products, in terms of manufacturing, quality controls, and pharmacovigilance. However, exceptions are granted when ATMPs are manufactured in hospitals.

As is often the case with regulatory exemptions, the EU's Hospital Exemption has been adopted because of specificities and special needs. In other words: "The exemption was included in the Regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals, which argued for a degree of flexibility over the nature of regulatory requirements" [13]. Furthermore, as the industry may eschew the development of some therapies of risky development processes and unclear intellectual property prospects, hospitals may have to fill the gap by taking on the manufacturing responsibility [29]. Finally, in some rare disease areas, patient populations may be too small for the conduct of classical clinical trials, which can be solved by delivering the therapy under a Hospital Exemption [30], thus speeding up access to therapies that might take too long to be approved via traditional routes [33]. For these reasons, the European regulation allows the use of an exemption, so that hospitals manufacture and deliver some therapies as unlicensed products, that is, products that do not have a marketing authorization.

It has been claimed, especially by industrial players, that regulatory exemptions may create potentially harmful loopholes. The Hospital Exemption is sometimes said to "constitute a disincentive to develop ATMPs to current regulatory and manufacturing standards" [27]. To be sure, the EU's exemption allows manufacturers to follow flexible pathways in terms of therapy risk-centred assessment [29] and efficacy criteria [32]. However, those who are exempt still need to keep high standards for patients [27], as well as comply with traceability, quality, and pharmacovigilance standards for ATMPs [31, 32]. Indeed, regulatory exemptions never amount to full regulatory freedom and could better be described as a special zone in the regulated field, as illustrated in Figure 1A.

Figure 1 appears here

Figure 1. The role played by exemptions in regulatory frameworks

Activities in the regulated area follow all the regulatory requirements whereas in the exempted area, they are not unregulated but are "subject to less regulatory intensity" [23] for some specific reasons. This does not allow us to hastily conclude that unlicensed medicines are riskier than the ones with a marketing authorisation. Such conclusion would need to be supported, for

example, by the conduct of a systematic study comparing the occurrence of severe adverse reactions in unlicensed and marketed medicines, with all the methodological complications that this kind of study would entail. Both classes of medicines are approved and overseen by regulatory agencies, which, in both cases, strive to make sure that patients can access therapies with as few risks as possible. If regulators decide to provide some manufacturers with some exemptions, this is due to the very specific characteristics of some products, which may, for example, target too small patient populations or require variable and tailored manufacturing processes.

Therefore, the EU's Hospital Exemption is grounded, on the one hand, on clinical needs, and this is why the exempted therapy should be manufactured "[...] under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient" [6]. On the other hand, the unlicensed therapy should be produced in exceptional circumstances, being recognized that it will be "prepared on a non-routine basis" [6].

However, considerations other than clinical needs can be taken into account when regulations are designed or revised. In the UK, a new rationale is emerging for a standalone regulation of point-of-care manufacture, as explained below.

B. The UK landscape

The UK has had, since 2010, two exemption schemes for bedside manufacture: its domestic Specials scheme and the EU's Hospital Exemption. The former has been much more frequently used than the latter. According to Interviewee 28, based in the MHRA, so far a Hospital Exemption has been obtained by only one British site, namely the Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust. However, because the EU law brings no precise regulatory definition for non-routine manufacture, there are doubts about the volume of therapies that can be produced under this scheme. In a written communication with the Cell-Therapies facility of the Trust mentioned above, we found out that this uncertainty was the reason why its Hospital Exemption was subsequently converted into a licence under the Specials scheme, with less doubts in terms of quantities manufactured.

In EU Member States, Hospital Exemptions have not been numerous but have been used more frequently than in the UK. In their 2020 study, Coppens and colleagues [29] identified, for example, eleven exemptions given in France, eleven in Netherlands, and seven in Germany.

In the UK's case, there are two reasons for the underutilisation of the Hospital Exemption. First, the Specials scheme is older than the Hospital Exemption, being therefore more familiar to British organisations. Indeed, companies and not-for-profit organizations attached to NHS Trusts have been created for manufacturing, exclusively, unlicensed medicines under the Specials scheme. There is even an Association of Pharmaceuticals Specials Manufacturers, now with twelve companies, including some non-British players⁴. Interviewee 2, a representative of this Association, explained that in order for companies to become members, “[...] the bulk of their commercial activity should involve the manufacture of unlicensed medicines.” Second, the Specials scheme, compared to the Hospital Exemption, contains some additional authorizations [13, 14]. The MHRA's guidance [13] spells out these authorizations, which are present in the scheme and absent in the EU's exemption: licence holders can import therapies that are also unlicensed in other countries; the therapy may be commissioned by dentists and supplementary prescribers; and the therapy can be administered outside hospitals, at locations not specified by the regulation.

In this way, the UK's regulatory landscape has taken the form depicted in Figure 1B; there is, on the one hand, the EU's scheme (Exemption) and, on the other hand, a further withdrawal of regulatory requirements (a sort of “Special exemption”) promoted by the British scheme.

Like the EU's exemption, the UK scheme is based on clinical demands, as therapies must be manufactured “to meet the special needs of individual patients” [13]. For this reason, the prescription of such therapies is subject to guidance from the General Medical Council, an independent body which sets clinical standards [34]. Furthermore, the prescription may be made only if there is no licensed therapy on the market for the particular disease [34].

With this format, the Specials scheme has attracted a variety of licence holders. In January 2021, 56 institutions held these manufacturing licences, most of which were obtained at an early period (from 2007 to 2010). Most of these licence holders are NHS hospitals or Trusts, as shown in Table 3.

⁴ <https://www.apsm-uk.com/>

Table 3. Specials licence holders, by nature of institution: January 2021

License holders	Number
NHS trusts	26
Private companies	24
NHS hospitals	3
Universities	3
TOTAL	56

The high proportion of Trusts and hospitals licenced under the Specials scheme suggests that private companies are leaving manufacturing gaps to be filled by clinical institutions. For instance, Interviewee 38, based in an NHS Trust, explained why this institution decided to manufacture unlicenced medicines in a unit located in a hospital: “Because they tend to be products that are not used enough to make it worthwhile investing to get a product licence.” This holds not only for relatively simple products but for ATMPs as well. For example, the Newcastle upon Tyne Hospitals NHS Foundation Trust has used its Specials licence for manufacturing a sight-saving product for an eye condition called limbal stem cell deficiency, as there is no licenced product on the market⁵. Furthermore, some ATMP areas tend to be underexplored. For example, Dimitropoulos and colleagues [30] claimed that companies are unlikely to focus on cell therapies for severe burns, which are not profitable enough for the industry.

Institutions with a Specials licence must declare where their manufacturing activities will happen. In January 2021, there were 71 manufacturing sites registered, as shown in Map 1.

⁵ <https://www.newcastle-hospitals.nhs.uk/news/newcastle-patients-first-to-receive-sight-saving-stem-cell-treatment/>

Map 1 appears here

Map 1. Sites where unlicensed medicines (Specials scheme) may be manufactured:

January 2021

For the production of Map 1, we considered only licences given from 2007, the year when the EU's ATMP Regulation was approved. In addition, we are considering only the MHRA's categories numbered from 1.3.1.1 through 1.3.1.7, encompassing: blood, immunology, cell therapy, gene therapy, biotechnology, human or animal extracted, and tissue engineering. These are, roughly, the categories also covered by the EU's ATMP legislation. (The limitation of our map is that institutions may be licenced but have no actual manufacturing activity. However, given the administrative work and economic investment required for obtaining a licence, it is fair to consider that these players are at least planning to perform some manufacture, unless they are using their licences only to import unlicensed products from other countries.)

Of the 71 sites seen on Map 1 (represented by dots), 40 are Trusts or hospitals, constituting hospital-centred manufacture. An interesting case is provided by Biotherapy Services⁶, a company offering a medicinal blood product (not considered as ATMP) for treating complex and chronic wounds that has been manufactured under the Specials scheme. Even though this company is not offering an ATMP, its manufacturing system has many characteristics of what the MHRA sees as point-of-care manufacture, especially the very short shelf life of its products, which amounts to less than twenty seconds. According to MHRA's data, the company had, in January 2021, six hospitals registered as manufacturing sites on its licence, but this list is constantly updated. As explained by Interviewee 6, a Biotherapy Services employee: "To retain a site, we would need to hold equipment there, and routinely audit or attend the site to keep it ready to go. If we know we'll be very infrequently at a site, the upkeep becomes too much of a resource drain." Thus the Specials scheme, although useful, has displayed some limitations, especially for companies that need to constantly update their list of manufacturing sites.

⁶ <https://biotherapyservices.com/>

Another of its weak points is the fragmentation it creates. As the Specials licence is strictly bound to particular sites, it is frequently difficult to diffuse promising products and projects, a typical feature of regulatory exemptions. Speaking of the EU's Hospital Exemption, Interviewee 1, a European regulator, made this point: "[...] those things very, very rarely move out of that particular hospital, and if the Professor who does it retires, it disappears." Therefore, regulatory exemptions may lead to regulatory fragmentation, as it is frequently difficult for exempted players to engage in collaborations and mutual support.

This difficulty has been noted before. Beck [22], for example, claimed that in federalist countries, regulatory exemptions subject organisations to state or local rules that foster local solutions. Even though the EU is not a classical federalist union, it has features of federalist political organisation, as noted by some authors [35-37]. In this sense, the Hospital Exemption would promote regulatory disintegration by transferring key decisions to Member States. If, on the one hand, this creates a flexible regulatory scheme, the resulting landscape can, on the other hand, prove piecemeal. For the EU's Hospital Exemption, it has been stressed that Member States have transposed Article 28 into national regulation in disparate ways [12, 29, 31]. Thus, regulatory exemptions might be inappropriate when one expects, and wishes to promote, a controlled diffusion of technologies and products. This is one of the reasons why the UK's MHRA has proposed a new regulatory framework where a particular modality of hospital-centred manufacture is no longer managed by means of exemptions, as we see in the sequence.

POINT-OF-CARE MANUFACTURE: THE MHRA'S REGULATORY FRAMEWORK PROPOSAL

In Table 1, it was seen that one of the main characteristics of point-of-care manufacture is the use of portable manufacturing devices. Interviewee 11, based in Cancer Research UK, gave the following description:

[...] you are literally manufacturing the pharmaceutical in the hospital environment or in an outpatient care centre, with the patient right there. So, if you think about dialysis. Dialysis uses a medical device which attaches to a patient [...] So, blood is drawn from a patient, it is changed in the process, and then it is reintroduced into the patient. In many respects we could consider a point-of-care manufacture [...] in the same way. You could be

producing the biological drug or a small molecule even if you're, like, within a small device or a set of devices which mimic your manufacturing plant or your process.

As explained by Interviewee 17, based in University College London, this kind of highly automated manufacture has been attempted, at clinical trial level, in some hospitals of different countries. It is an emerging approach that “makes the patient part of the supply chain” [38].

In 2020, the MHRA organised two consultation meetings with specialists in the field, aiming to identify the challenges of point-of-care manufacture, as defined in Table 1. At the beginning of 2021, an additional online workshop was held to introduce the main lines of its regulatory proposal⁷. In mid-2021, a public consultation was carried out. Elsewhere [5], we described this process and outlined the regulatory framework, which is also briefly presented below.

One of the guiding considerations of the proposal is that for some products, including some ATMPs, the shelf life (that is, the length of time for which the product remains viable and safe after its production has been completed) will be short (some days), or extremely short (hours, minutes or seconds). This is so because manufacturers may need to handle cells and tissues whose therapeutic potential is minimised or destroyed if the product is frozen for transportation. Other products have short life spans, being incapable of surviving long periods outside the human body, as is the case of pancreatic islets [39]. In this way, manufacture must happen near the patient, being performed close to the hospital or even within it, sometimes very quickly. As explained by Interviewee 28, an MHRA regulator: “[...] you now have to go from your [manufacturing] room, up the corridor, to the operating theatre, you've got [...] seconds to do that [...].”

The MHRA also considers that for some products, manufacturing capacity and activities may be spread across a large number of hospitals. Some days prior to the 2021 workshop, the agency circulated a regulatory proposal document. One of the points made there is: “An application currently at clinical trial stage is projected to involve approximately 200 [...] sites in the UK, which would manufacture a total of about 12,000 products per year” [40]. With such large number of sites, the MHRA's inspection capability would be put under much strain.

To face these challenges, the agency has proposed the new regulatory framework for point-of-care manufacture, as illustrated in Figure 2.

⁷ Members of our research team participated in all those meetings.

Figure 2 appears here

Figure 2. The MHRA's regulatory proposal

Source: [41]

In this model, the key player is the so-called Control Site, the institution (probably, a private biotech or pharma company) responsible for various tasks: procurement of starting materials, manufacture, quality control, inclusion and exclusion of Manufacturing Sites, inspection of sites, traceability, and so on. Here we are no longer dealing with a regulatory exemption; thus the Control Site is expected to obtain a clinical trial authorization, run the trial, and eventually get a marketing authorization for the product, which will be sold as a commercial medicine [17, 41].

Communication between the Control Site and Manufacturing Sites will take place through a reporting system whose sophistication will depend on the product's characteristics. When high risks are present, the system may involve real-time communication so adverse events can be reported with no delay. The Control Site will keep the MHRA informed about all the relevant aspects by means of a Point-of-Care Master File. This document, whose contents are yet to be fully specified, will contain information such as product properties, Manufacturing Sites details, adverse events, and GMP inspections [17, 41]. The MHRA also wishes to create a framework where site management is dynamic and simple, so the Control Site can "[...] add new manufacturing sites in order to increase manufacturing capacity [...], without the lengthy and expensive regulatory processes of repeatedly updating clinical trial or marketing authorisations and manufacturing authorisations" [42].

The MHRA is willing to create a framework that can be functional for a very broad range of products, from relatively simple medicines to ATMPs. For this reason, the agency points out its openness to adjust various aspects of the system, according to more precise guidelines to be published once the framework has been passed into law (probably in the course of 2023). For example, in the public consultation, the MHRA [17] declared: "Data requirements for finished product testing, batch analyses, stability testing and labelling will be dependent on the nature of the product and the shelf life; these could differ significantly from conventional pharmaceuticals

and may need to be agreed on a case-by-case basis.” Other elements that may be subject to adjustments include the frequency of site inspections, the contents of the Master File, and the format of risk management plans.

In this way, the MHRA is proposing a proportionate approach for its framework regulation, with features of so-called “adaptive regulation” [43, 44] whereby requirements are adjusted when new knowledge becomes available. The approach also has some aspects resembling “enforced self-regulation” [45, 46], also known as “management-centred regulation” [47], whereby regulated entities help establish the parameters for risk management and quality control.

This flexibility announced by the emerging regulatory framework seems to be well-regarded by both the industry and academic players in the field. In the workshop we held in June 2021, participants were polled on what they considered as the strongest aspect of the MHRA’s proposal. We received feedback from 17 participants, as summarized in Chart 1.

Chart 1 appears here

Chart 1. Strongest aspect of the regulatory proposal, according to 17 workshop participants:

June 2021

After the concept of Control Site, the aspect most appreciated was precisely the proposal’s flexibility. It can then be argued that the MHRA is designing a regulatory landscape (as illustrated in Figure 1C) where the regulated area is split into two zones, one with strict requirements leading to marketing authorizations and post-market surveillance (for conventional centralized manufacture) and another one (for point-of-care manufacture) where the agency can adjust requirements to make them fit a variety of situations, products, and manufacturing systems. Stringent requirements are then combined with a regulatory flexibility generally obtained via exemptions, and the outcome is a sort of “Exceptional regulation” zone (Figure 1C). At the same time, the exemption area (for bedside manufacture) will be kept, because as explained by Interviewee 28 (MHRA), the Specials scheme will not be extinguished. “[...] we can’t force people

and say: ‘Right, you’ve got to stop now this unlicensed [production]; you’ve got to apply for a marketing authorisation.’ They’ll just walk away.”

Once again, the MHRA, by maintaining the Specials scheme, is not subjecting some patients to unnecessary risks. There will be risks associated with any category of medicines, whether they are unlicensed or sold commercially, especially when it comes to ATMPs. With the continuation of the Specials scheme, the MHRA is guaranteeing that some medicines not yet explored by the industry can be produced, with as few risks as possible, bearing in mind that clinicians may need to produce medicines requiring very bespoke and variable manufacturing procedures.

The MHRA’s framework proposal summarised above is inspired by concerns that had been absent in regulatory exemptions for bedside manufacture. The rationale of the Specials exemption is based on medical needs “[...] and does not include reasons of cost, convenience or operational needs” [34]. In its turn, the emerging point-of-care authorisation is decisively informed by technical and operational considerations, namely the short shelf life of products and the diffusion of manufacture across many sites. Therefore, this regulatory shift, with a marketing authorization being made to coexist with exemption schemes, implies the creation of a new rationale, in addition to generating concerns and debates which are briefly highlighted in the next section.

REGULATORY RATIONALES AND STRATEGIC DECISIONS

As explained above, the MHRA has proposed a regulatory framework highly informed by technical and operational considerations. The latter are surely key but there is much more to point-of-care manufacture. In the literature, as well as the interviews we have conducted, various other issues have been highlighted and some grey areas of the MHRA’s proposal have been identified, especially with regard to its on-the-ground implementation and enforcement. The remaining parts of this section provide a brief description of some of these issues.

A. Infrastructure and investments

When discussing the MHRA’s proposal, some interviewees highlighted that, for the most part, the role of Control Site will be played by middle-sized and large companies. This expectation

is sometimes coupled with the view that researchers based in university hospitals are frequently not prepared to develop and manufacture products in the most robust and effective ways. As claimed by Interviewee 1, a European regulator:

[...] when they arrive to us, with an academic dossier, you don't know where to start. You know, you don't have a single patient that you can compare with the other, because you have tried different things in all of them [...] The companies do it the other way around. "Don't change anything. We'll do a full batch, compare the batch, we need to know all the parameters of solubility, viability, the reagents, the number of hours, the conditions of the incubator, we can scale it up, we can have, you know, the potency assays..." The academics just don't think that way.

Nevertheless, there have been some successful projects conducted by clinicians-academics. In Spain, at the Hospital Clinic of Barcelona, for example, a CAR-T cell product (which derives from gene-editing technology and fights drug resistant cancers) has been manufactured and delivered to patients since 2017. Nowadays, around forty patients receive the product every year. According to Interviewee 5, a member of this clinical team, the project's main advantage is medical autonomy, as the team has full control over the process, from collection of starting patient samples to administration of the final product. For this product, the Spanish team is using a Hospital Exemption, capitalizing on its less stringent requirements in terms of data collection and efficacy parameters.

In its turn, the UK's emerging framework brings the rationale of marketing authorizations to hospital-centred manufacture. If many companies end up acting as Control Sites and routinely visiting hospitals with their portable systems to perform manufacturing activities, hospitals will need to implement changes in terms of available technologies and staff [3], enhancing their preparedness or "institutional readiness" [48]. In addition, it will be necessary to establish workflows and standard operating procedures for handling materials, liaising with manufacturers and couriers, scheduling patients, and so on. These demands can become particularly pressing in the largest hospitals, which may be mobilised, as Manufacturing Sites, for a range of products on a daily basis. Elsewhere [49], we showed how the rules and standards of clinical trials bring to hospitals rigid mandates in terms of skills management, contract clauses, and physical space. Equally, the UK's emerging framework can potentially introduce new demands and pressure into the premises of NHS settings turned into manufacturing units of commercial products.

In the field of ATMPs, regulatory requirements have caused drastic redefinitions of public entities' scope of actions. It has been claimed, for example, that the EU's ATMP Regulation has expanded market opportunities but restricted the range of actions available to public hospitals and research institutions [50]. While the UK's emerging framework raises questions about the role to be played by companies (as a potential key group of Control Sites), the adaptations required from hospitals seem to be even more drastic, as some of the manufacturing activities taking place in their premises are to be covered by requirements to which only market players are fully accustomed. Possibly, they will be witness to the installation of new standards, data management systems, auditing procedures, and others practices whose impact on routine clinical activities is yet to become clear.

B. The strategic value of hospital-centred manufacture

Academic or clinical teams manufacturing ATMPs in a hospital explain that one of the advantages of such endeavour is that in the medium or long term, the hospital is able to save costs [7, 51]. According to Interviewee 5, a clinician-researcher based in the Clinic Hospital of Barcelona, where a CAR-T product has been manufactured, the therapy's price is around one-quarter of the average price of the CAR-T product which the health system would have to otherwise purchase from the industry.

However, the economic effects of ATMP hospital-centred manufacture are controversial. For Interviewee 17, a researcher based in University College London, hospital-centred manufacture of cell and gene therapies is likely to be more economically sustainable when hospitals partner with companies or when adjacent manufacturing facilities, run by technology companies, are built up. This interviewee concluded: "I think there's a need for clinical trial manufacture [...], which I can see some benefit and argument for. But for routine manufacture, I don't think a hospital can sustain that activity, and it's a very, very different skillset that's required."

This view, according to which hospital-centred manufacture of ATMPs should be market-driven, seems to prevail in the UK. Administrators of hospital manufacturing facilities, including the largest and most experienced institutions such as NHS Blood Transplant (NHSBT), prefer to shun ATMP production when it does not target clinical trials. The NHSBT, for example, runs GMP manufacturing facilities in six cities, including one in a hospital in Oxford. Interviewee 31, a NHSBT employee, explained that the institution would be reluctant to be involved in ATMP

manufacture not related to preclinical or clinical trials, because in addition to the costs involved, it would be necessary to engage in an unknown regulatory field, including building capacity related to risk management and liability issues.

The MHRA's emerging point-of-care manufacture framework can strengthen or solidify such views and expectations, as it introduces the need for running costly clinical trials and obtaining marketing authorisations. Eventually, hospital administrators, policymakers, and entrepreneurs operating in the UK might eventually be convinced that investments in the hospital-centred manufacture of licenced ATMPs should be always carried out by those players already used to develop commercial products. Moreover, it can be claimed that the MHRA's proposal is creating a market opportunity, as it introduces or enhances the distinction between bedside and point-of-care manufacture, providing the latter with a clear marketing authorization route, in a move appreciated by the industry.

In the 1980s and 90s, NHS Trusts decided to create some manufacturing organizations, such as Torbay Pharmaceuticals⁸ and Newcastle Specials⁹, which are now providing routine, non-ATMP medicines to several hospitals across the UK, frequently filling market gaps. This has been possible thanks to the regulatory exemption constituted by the UK Specials scheme, as well as the decisions made, at that time, to provide NHS Trusts with manufacturing capacities, technical skills, and regulatory compliance expertise that seemed strategic. Nowadays, a new phase is emerging in which ATMPs can, and in some cases must, be subjected to hospital-centred manufacture. Once again, the resulting landscape will depend on how regulations are designed and investment decisions made. As for investments, the UK has witnessed a decade of declining public spending in its health system [52]. In this context, one might hope that the lack of government investment could be offset by the investments made by Control Sites willing to visit Manufacturing Sites and mobilise miniaturized manufacturing systems, in a new model of commercial mobile therapy provision. In terms of regulations, the nascent framework proposes to subject point-of-care manufacture to requirements and licensing pathways that are more familiar to companies than hospital researchers. In this way, the MHRA's regulatory proposal is made in a context where the technical, operational, and commercial challenges of hospital-centred manufacture (in its two modalities) are clearly identified, but its strategic value, from the viewpoint of public healthcare policies and technology governance strategies, tends to be neglected.

⁸ <https://torbaypharmaceuticals.nhs.uk/>

⁹ <https://www.newcastlespecials.co.uk/>

CONCLUSION

Exemptions have been used by regulators to account for the diversity of players subjected to the law. In this way, they can be considered as instruments which promote regulatory precision [21, 24] and social welfare [20], showing that “exemptions are not just random loopholes” [22].

Precisely because of the flexibility they provide, exemptions have been adopted in the regulation of ATMP manufacture, especially when such manufacture happens in hospitals or other clinical settings. Key examples have been the EU’s Hospital Exemption (part of the ATMP Regulation) and the UK’s Specials scheme.

Expecting to observe a rise in hospital-centred manufacture in the years to come, and wishing to regulate such activities in a more precise and dynamic way, the UK’s MHRA is now proposing a new regulatory framework for point-of-care manufacture. The proposal brings the concept of Control Site, the institution that will be responsible for the overall management of the manufacturing system, taking the product from the development phase, through clinical trials, to the stage of licenced medicine. In this way, a regulatory domain is being created where point-of-care manufacture ceases to follow the rationales of exemptions to follow those of marketing authorizations.

In this article we have analysed this process aimed to generate a new regulatory framework. From a theoretical point of view, it is interesting to see how the MHRA makes efforts to take a branch of hospital-centred manufacture (point-of-care manufacture) towards the logic of marketing authorizations while keeping the regulatory flexibility that will be needed to oversee manufacturing systems populated with diverse companies, hospitals, and technical solutions. In doing so, the MHRA proposes a proportionate and adaptive framework (or a zone of “Exceptional regulation” as we was called it in Figure 1C) where expectations and requirements will be highly dependent on the product’s characteristics and associated risks.

From a practical point of view, most interested players, such as experts and practitioners based in companies, academic departments, and even NHS pharmacies, welcome the regulatory change, as pointed out by the MHRA [42]. At the same time, however, some issues of concern have been detected in our study, such as the differences between hospitals and the readiness of different institutions for the emerging framework. In this way, when the regulatory proposal goes through the parliamentary process and is subjected to political assessment, some of its key concepts and

proposals may change either slightly or substantially. Even if the proposal passes as is, both companies and NHS Trusts may prefer to continue to use the Specials scheme and produce unlicensed medicines. Thus the upcoming regulation may turn out to be of little impact in spite of its innovative nature. As explained by Fuller [53], laws can “fail,” and they do so when they posit requirements that cannot be followed by those supposed to follow them.

The rationale of exemptions, which prevails in the Specials scheme, can generate regulatory fragmentation, in the sense that different procedures, quality standards, and data management systems are put in place in different hospitals. Thus, it may be too difficult, or even impossible, to disseminate solutions that are working well in particular settings. In this respect, the MHRA’s proposal can be very helpful to promote higher levels of standardization and technical efficiency, fostering the dissemination of promising ATMPs.

At the same time, however, it is important to strike a good balance between operational and technical requirements, on the one hand, and the medical reasons that have been the main motivators of both the EU’s Hospital Exemption and the UK’s Specials scheme, on the other. As the proposal goes through the parliamentary process, the interests of key stakeholders are likely to sharpen, impacting political choices that will define the models with which ATMPs will be developed, distributed, and (hopefully) accessed in the years to come.

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