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FULL-LENGTH ARTICLE

Regulatory Policies

Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries

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ABSTRACT

Background aims: As part of the advanced therapy medicinal product (ATMP) regulation, the hospital exemption (HE) was enacted to accommodate manufacturing of custom-made ATMPs for treatment purposes in the European Union (EU). However, how the HE pathway has been used in practice is largely unknown.
Methods: Using a survey and interviews, we provide the product characteristics, scale and motivation for ATMP manufacturing under HE and other, non-ATMP-specific exemption pathways in seven European countries.
Results: Results show that ATMPs were manufactured under HE by public facilities located in Finland, Germany, Italy and the Netherlands, which enabled availability of a modest number of ATMPs (n = 12) between 2009 and 2017. These ATMPs were shown to have close proximity to clinical practice, and manufacturing was primarily motivated by clinical needs and clinical experience. Public facilities used HE when patients could not obtain treatment in ongoing or future trials. Regulatory aspects motivated (Finland, Italy, the Netherlands) or limited (Belgium, Germany) HE utilization, whereas financial resources generally limited HE utilization by public facilities. Public facilities manufactured other ATMPs (n = 11) under named patient use (NPU) between 2015 and 2017 and used NPU in a similar fashion as HE. The scale of manufacturing under HE over 9 years was shown to be rather limited in comparison to manufacturing under NPU over 3 years. In Germany, ATMPs were mainly manufactured by facilities of private companies under HE.
Conclusions: The HE enables availability of ATMPs with close proximity to clinical practice. Yet in some countries, HE provisions limit utilization, whereas commercial developments could be undermined by private HE licenses in Germany. Transparency through a public EU-wide registry and guidance for distinguishing between ATMPs that are or are not commercially viable as well as public-private engagements are needed to optimize the use of the HE pathway and regulatory pathways for commercial development in a complementary fashion.

Introduction

Gene- and cell-based therapies (GCTs) are a heterogeneous group of medicinal products that hold great potential to improve health care. They offer new modalities for treatment compared with pharmaceuticals (i.e., small molecules and biologics), in particular for therapeutic areas in which current treatment is lacking or has unsatisfactory clinical outcomes [1]. For instance, GCTs have the potential

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to regenerate damaged or lost tissue and provide new treatment modalities for autoimmune diseases, cancers and monogenetic disorders [2,3]. GCTs, defined as advanced therapy medicinal products (ATMPs) in the European Union (EU), are regulated as medicinal products and marketed through the central authorization procedure in the EU. Yet reports of hurdles in reaching patients through commercial development are numerous [1,4–9]. This is partly due to their complex product characteristics and scientific uncertainties that challenge commercial development and regulatory pathways [10]. Moreover, many ATMPs are rooted in clinical practice [11], and early clinical developments are largely undertaken by academic hospitals [12]. Yet it is reported that academic hospitals and other public institutes struggle to complete developments all the way to the market through the centralized authorization procedure [8,13,14].

There are three EU regulatory pathways (i.e., exemption pathways) that exempt ATMPs from the centralized authorization pathway: hospital exemption (HE), named patient use (NPU) and compassionate use (CU). HE enables manufacturing of ATMPs only (not other medicinal products) for treatment purposes outside of clinical trials because it exempts ATMPs from clinical trial regulations and the centralized pathway for authorization of ATMP Regulation EC1394/2007 under specific conditions. It accommodates manufacturing of "custom-made" ATMPs on a "non-routine" basis for treatment purposes in hospital settings (ATMP Regulation, Article 28) [15,16]. NPU and CU are historically used for the manufacturing of all types of medicinal products outside of clinical trials. These pathways facilitate early access to investigational medicinal products for patients in need that are not enrolled in a clinical trial [17]. NPU enables manufacturing of investigational medicinal products for individual patients in need of treatment in accordance with the specifications of a health care professional (Directive 2001/83/EC, Article 5). In addition, investigational medicinal products (not limited to ATMPs) can be manufactured for compassionate use while these are in clinical development under CU pathways (Regulation 726/2004, Article 83). Manufacturing under CU pathways can provide early access to larger groups of patients [17]. HE, NPU and CU are all authorized on a national level by the competent authorities of EU countries. Moreover, the competent authorities of EU countries are responsible for translating EU legislation into national law, resulting in an array of national exemption pathways and regulatory provisions across the EU [17,18]. Previous work highlights marked differences in evaluation criteria for approval of HE licenses, ranging from relatively simple manufacturing and quality criteria to more stringent requirements for clinical data and restrictions to eligible license holders [18]. Yet whether and how these pathways are used to actually manufacture ATMPs without central authorization, outside of clinical trials, is largely unknown.

Work published in 2012 showed that in numerous EU countries (except Germany and the Netherlands), HE had not yet been used for ATMP manufacturing [19]. More recent studies indicate that HE utilization has increased over time and expanded to a few other countries, including Finland and France [18,20]. Different types of ATMPs are manufactured under HE, including lymphocytes, chondrocytes, dendritic cells and stem cells [20]. Public stakeholders have stated that HE is particularly suited to manufacturing ATMPs with historic experience in clinical practice as well as ATMPs that target ultra-rare diseases [8,18,21,22]. However, the scale of manufacturing, the characteristics of targeted patient populations (e.g., indication) and the motivation for facilities to manufacture under the HE pathway are largely unknown. Regulators recently reported that public ATMP manufacturing facilities experience difficulties complying with national provisions for HE [18], which could impede ATMP manufacturing and treatment within clinical practice [8,14,23]. Furthermore, companies can apply for HE licenses in numerous EU countries [18]. In addition, there are indications that alternative exemption pathways are preferred over the HE pathway in some countries, such as the specials scheme (i.e., NPU pathway) in the UK [18,21].

In this study, we investigate ATMP manufacturing under HE in practice. We first provide insights into product characteristics and the scale of ATMP manufacturing and treatment under HE and other exemption pathways. Furthermore, we provide insights into the motivation to manufacture ATMPs under HE and other exemption pathways. The comparative analysis includes manufacturing activities of public and private ATMP facilities that are located in seven EU countries (Belgium, Finland, France, Germany, Italy, the Netherlands, UK). Provided insights may substantiate debates on the impact of HE on ATMP availability in clinical practice and on commercial ATMP development.

Methods

Selection of ATMP manufacturers

We selected ATMP manufacturers in European countries that (i) were Member States of the EU, (ii) implemented regulatory provisions for HE by June 2018 and (iii) showed indications of ATMP clinical activity, evidenced by the conduction of clinical trials [24] or ATMP manufacturing under HE [19]. Based on these criteria, we initially selected nine countries (Austria, Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, UK) for the purpose of this study.

In the selected countries, we attempted to identify all public ATMP manufacturing facilities (i.e., hospitals as well as blood and tissue banks, henceforth referred to as public facilities), regardless of regulatory pathways, and all private HE license holders (i.e., commercial entities, henceforth referred to as private facilities). The ATMP working group of the Netherlands and Flemish academic medical centers as well as ATMP experts from the other selected countries were consulted to identify public facilities in their respective country. Based on a snowball approach, we identified public facilities in seven countries (Belgium, Finland, France, Germany, Italy, the Netherlands, UK). We were not able to obtain contact information for hospitals in France or public facilities in Austria and Spain. However, previous work showed that no HE licenses were granted in the latter two countries up to June 2018 [18]. Therefore, manufacturing in Austria and Spain is not further described. In addition, we identified all private facilities in the nine selected countries, building on previous engagement with competent authorities and public regulatory information [18].

Data sources

We used a mixed-methods approach to collect data on ATMP manufacturing under exemption pathways. First, we used public sources to identify public and private HE license holders, which were found for France [25] and Germany [26] only. Second, we collected data from public facilities through a survey, which depended on the availability of survey respondents, followed up with interviews. We collected data from private facilities through interviews only.

Data collection

We collected data from the identified public facilities with a survey that was developed using the LimeSurvey platform belonging to the Utrecht Pharmacy Practice network for Education and Research [27]. The work was conducted in compliance with the requirements of the Utrecht Pharmacy Practice network for Education and Research Institutional Review Board of the Department of Pharmacoepidemiology and Clinical Pharmacology. We assigned entry codes for each facility, which allowed both anonymization of individual respondents and identification of facility and country. The survey was sent out per

country in a staggered manner between November 2018 and March 2019.

The survey consisted of two parts to distinguish between ATMP manufacturing under HE versus other exemption pathways (i.e., named patient use, compassionate use). The period of analysis for manufacturing under HE ranged from January 1, 2009, to December 31, 2017. The period of analysis for ATMP manufacturing under other exemption pathways was restricted to January 1, 2015, to December 31, 2017, because documentation for NPU manufacturing activities before 2015 was foreseen to be potentially less accessible to facilities and lead to non-responses.

The survey consisted of questions and pre-filled checkboxes per product (Table S1) for ATMPs that had been manufactured under exemption pathways. HE licenses that were not used for manufacturing were not included. Entries directly related to product characteristics, scale and motivation to manufacture under exemptions. Product characteristics entailed the product type (i.e., ATMP classification), origin of cellular starting material, proposed active substance and targeted therapeutic area of the manufactured ATMP. Scale entailed the scale of manufacturing, scale of patient treatment and period of manufacturing. Finally, respondents could select one main reason to motivate their choice to manufacture the ATMP under the used exemption pathway. For possible entries per variable, see Table S1.

All survey respondents were invited to participate in a short follow-up interview by telephone. A semi-structured questionnaire was used to discuss (i) survey entries for the ATMPs that were manufactured under exemption pathways (if applicable) and (ii) their motivation to manufacture under HE, other exemption pathways or clinical trials (whichever was applicable to the facility). Interviews were conducted between February and March 2019. All interviewees were employees of their public facility.

Chief executives or executives of regulatory or manufacturing departments of private facilities were also invited for interviews by telephone. A semi-structured questionnaire was used to discuss (i) the product characteristics and scale of ATMP manufacture under HE (similar to the survey) and (ii) their motivation to manufacture under HE. Interviews were conducted between February and March 2019. Oral consent for recording was sought before all interviews with public and private facilities began. Recordings were used to create minutes of the interviews.

Data analysis

Responses from the public facilities were first tabulated to capture the survey response rate and number of ATMPs manufactured under exemption pathways per country. Second, data for each ATMP manufactured under exemption pathways by public facilities were categorized according to a set of pre-defined variables and values to determine product characteristics, scale of manufacturing and treatment and main reason to manufacture under an exemption pathway (Table S1). We subsequently conducted a descriptive sample analysis based on the assigned values by tabulating and stratifying data by regulatory pathway and country, using IBM SPSS Statistics 24 (International Business Machines Corporation, Armonk, NY, USA). Product characteristics and scale of ATMP manufacturing under HE by private facilities were extracted from the interview minutes and tabulated. Because of the small numbers, statistical analysis was not performed.

To estimate the total patient exposure to exemption ATMPs, we calculated the sum of the minimum and maximum number of patients per range (Table S1) for all ATMPs per exemption pathway, stratified by public and private facilities. We assumed a range of 200 to a maximum of 500 patients for a range of more than 200 patients and one to a maximum of 500 patients when the scale of treatment was unknown. We did not correct for response rate (public facilities) or total number of HE license holders (private facilities) because presented data for HE for public facilities approached a complete data set in the selected countries and it is unclear whether all private facilities used their HE license for manufacturing.

Interview minutes were used to capture a more nuanced perspective on how facilities are motivated to manufacture under exemption pathways. Building on previous work on institutional readiness to adopt ATMPs in clinical practice [28,29], we developed a preliminary coding tree to capture the motivation for manufacturing under exemption pathways by coding reasons within the following categories: clinical needs, clinical skill base and expertise (e.g., historic experience in clinical practice, previous clinical trial conduct), regulation, financial resources, logistical and manufacturing capacities and professional/institutional interests [28,29]. After an initial round of open coding, a second round of axial coding was performed to group open codes into common, coded reasons (Tables S2–4).

For facilities that manufactured ATMPs under exemption pathways, we coded (i) reasons to manufacture under exemption pathways per manufactured product (i.e., product-specific reasons) and (ii) product-transcending reasons (i.e., non-product-specific) to manufacture under exemption pathways. For facilities that did not manufacture ATMPs under exemption pathways, we coded reasons (i.e., non-product-specific reasons) to not manufacture under exemption pathways. Coded product-specific reasons were extracted and stratified by regulatory pathway, tabulated and pooled for comparative analysis (Table S2). Coded non-product-specific reasons were extracted, tabulated and pooled for comparative analysis (Tables S3–4). To indicate differences in national provisions among the selected countries, we indicated in which countries reasons to manufacture or to not manufacture, in relation to regulation, were described. For other reason categories, the number of observations allowed reporting on an aggregate level only.

Subsequently, the motivation for private facilities to manufacture under HE was coded using the same approach as for public facilities and captured separately from the motivation for public facilities. Results were extracted, tabulated and pooled for comparative analysis. All qualitative analyses were performed using NVivo Pro v11 (QSR International, Melbourne, Australia).

Table 1
Survey response rate and number of ATMPs manufactured under exemption pathways by public facilities, per country.

	Public facilities		ATMPs (public)	
	Recipients (n)	Respondents (n)/response rate (%)	HE (n) 2009–2017	NPU (n) 2015–2017
Belgium	7	3/43	0	0
Finland	2	1/50	1	0
France	1	1/100	0	0
Germany	22	3/14	3	0
Italy	5	3/60	2	5
Netherlands	9	8/89	6	2
United Kingdom	21	8/38	0	4
Total	67	27/40	12	11

Results

Public ATMP manufacturing under exemption pathways

We identified 67 public ATMP manufacturing facilities in seven countries (Belgium, Finland, France, Germany, Italy, the Netherlands, UK). Of these 67 public facilities, 27 provided input to our survey (40% overall response rate). Overall, the respondent public facilities manufactured 12 ATMPs under HE between 2009 and 2017 and 11 ATMPs under NPU between 2015 and 2017 (Table 1). The survey respondents did not manufacture ATMPs under CU pathways.

Overall, seven public facilities manufactured 12 ATMPs (Finland n = 1/12, Germany n = 3/12, Italy n = 2/12, the Netherlands n = 6/12) under HE between 2009 and 2017 (Table 1). The other 20 respondent public facilities did not manufacture ATMPs under an HE license.

Manufactured ATMPs under HE were mainly somatic cell therapy medicinal products (n = 11/12), plus one combination ATMP (n = 1/12). No gene therapy medicinal products or genetically modified cell-based products were manufactured under HE. The origin of cellular starting material was mostly allogeneic (n = 8/12). Out of all possible proposed active substances (Table S1), ATMPs consisted of mesenchymal stromal cells (MSCs) (n = 8/12), hematopoietic stem cells (n = 2/12) and lymphocytes (excluding CAR T lymphocytes) (n = 2/12). These ATMPs mainly targeted diseases or conditions in the therapeutic areas of immunological diseases (n = 4/12) and hematology/oncology (n = 3/12). Other therapeutic areas included cardiovascular (n = 2/12), infectious (n = 1/12) and musculoskeletal diseases/conditions (n = 1/12) or were unknown (n = 1/12) (Table 2). MSCs mainly targeted immunological diseases (n = 4) and hematology/oncology (n = 2), hematopoietic stem cells targeted cardiovascular diseases/conditions (n = 2) and lymphocytes targeted infectious diseases (n = 1) and hematology/oncology (n = 1).

For most ATMPs manufactured under HE, the scale of manufacturing did not exceed 10 batches (n = 6/12) or 50 batches (n = 3/12) between 2009 and 2017. Yet for some, the scale of manufacturing was relatively large. For one ATMP in the Netherlands (n = 1/12), the scale of manufacturing ranged between 50 and 200 batches. In Germany, more than 200 batches were manufactured for two ATMPs (n = 2/12) (Table 2). The range of manufacturing largely overlapped with the range of patient treatment. Yet for one MSC product, a maximum of 10 batches was manufactured for treatment of over 200 patients (not shown), while for another MSC product more batches were manufactured (more than 200) compared with patient treatment (between 50 and 200). The manufactured batches were used to treat up to 10 patients (n = 5/12), up to 50 patients (n = 3/12), 50–200 patients (n = 1/12), more than 200 patients (n = 1/12), or the scale of treatment was unknown (n = 1/12). The patient exposure ranged from a minimum of 336 to a maximum of 1600 under HE.

Table 2
Scope and scale of manufactured ATMPs under exemption pathways by public facilities, per country.

Regulatory pathway	Hospital exemption					Named patient use			
Country	FI (n = 1)	DE (n = 3)	IT (n = 2)	NL (n = 6)	Total HE (n = 12)	IT (n = 5)	NL (n = 2)	UK (n = 4)	Total NPU (n = 11)
ATMP subtype									
Somatic cell therapy medicinal product	0	3	2	6	11	5	2	4	11
Combination ATMP	1	0	0	0	1	0	0	0	0
Origin of cellular material									
Autologous	1	1	0	2	4	2	0	0	2
Allogeneic	0	2	2	4	8	3	2	4	9
(Proposed) active substance									
Lymphocytes	0	1	0	1	2	3	1	2	6
Hematopoietic stem cells	0	1	0	1	2	0	0	0	0
Mesenchymal stromal cells	1	1	2	4	8	2	1	2	5
Target disease/condition									
Immunology	0	1	0	3	4	1	0	1	2
Infection	0	0	0	1	1	2	1	1	4
Cardiovascular	0	1	0	1	2	0	0	0	0
Hematology/oncology	0	1	1	1	3	2	1	1	4
Musculoskeletal	1	0	0	0	1	0	0	1	1
Unknown	0	0	1	0	1	0	0	0	0
Scale of manufacturing									
0–10 batches	1	0	2	3	6	2	2	1	5
10–50 batches	0	1	0	2	3	3	0	0	3
50–200 batches	0	0	0	1	1	0	0	1	1
More than 200 batches	0	2	0	0	2	0	0	0	0
Unknown	0	0	0	0	0	0	0	2	2
Scale of patient treatment									
0–10 patients	1	0	1	3	5	4	1	0	5
10–50 patients	0	1	0	2	3	1	1	1	3
50–200 patients	0	1	0	1	2	0	0	1	1
More than 200 patients	0	1	0	0	1	0	0	0	0
Unknown	0	0	1	0	1	0	0	2	2
Period of manufacturing									
2009–2015	0	0	1	1	2	NA	NA	NA	NA
2015–2017	0	0	0	3	3	5	2	4	11
Both periods	1	3	1	2	7	NA	NA	NA	NA
Main motivation for regulatory pathway									
Few patients to be treated	1	0	0	0	1	0	0	0	0
Clinical urgency to treat	0	2	1	1	4	4	1	0	5
Lack of alternative treatment	0	0	1	5	6	0	1	3	4
Continue availability	0	1	0	0	1	0	0	0	0
Data collection for clinical trials	0	0	0	0	0	1	0	0	1
Unknown	0	0	0	0	0	0	0	1	1

DE, Germany; FI, Finland; IT, Italy; NA, not applicable (period of analysis for other exemption pathways was restricted to 2015–2017); NL, Netherlands; UK, United Kingdom.

Most ATMPs were manufactured and used for treatment between 2009 and 2017 (n = 7/12). Two ATMPs were manufactured before 2015 (manufactured between only 2009 and 2015), whereas three others were manufactured after 2015 (manufactured between only 2015 and 2017) (Table 2).

The respondent German public facilities are part of the German blood bank, which is licensed under HE [26]. In France, there are five public facilities (hospitals) that together have seven HE licenses to manufacture a particular class of ATMP for national use (somatic cell therapy medicinal products, tissue engineering products, combination ATMPs). Furthermore, hospitals are licensed to manufacture HE products under the clinical trial framework [25]. Whether and to what extent these HE licenses are used for manufacturing in France is unknown and not described further.

Overall, five public facilities manufactured 11 ATMPs (Italy n = 5/11, the Netherlands n = 2/11, UK n = 4/11) under NPU pathways between 2015 and 2017. These are different products than the ATMPs manufactured under HE. Manufactured ATMPs were all somatic cell therapy medicinal products (NPU n = 11/11), mostly based on allogeneic starting material (n = 9/11). The ATMPs consisted of lymphocytes (excluding CAR T lymphocytes) (n = 6/11) and MSCs (n = 5/11). These ATMPs targeted mainly infectious diseases (n = 4/11) and hematology/oncology (n = 4/11). Other therapeutic areas included immunological diseases (n = 2/11) and musculoskeletal disorders (n = 1/11) (Table 2). Lymphocytes targeted infectious diseases (n = 4) and hematology/oncology (n = 2), and MSCs mainly targeted immunological diseases (n = 2) and hematology/oncology (n = 2) (not shown).

The scale of manufacturing under NPU did not exceed 10 batches (n = 5/11) or 50 batches (n = 3/11) for most ATMPs between 2015 and 2017. The scale for one ATMP manufactured in the UK ranged between 50 and 200 batches (n = 1/11). For two other ATMPs manufactured under NPU in the UK the scale was unknown (n = 2/11). The scale of patient treatment showed ranges identical to those of scale of manufacturing. The patient exposure ranged from a minimum of 87 to a maximum of 1400 under NPU (Table 2).

The survey allowed respondents to select one main reason to motivate ATMP manufacture under an exemption pathway. Results show that manufacturing under HE was primarily motivated by clinical needs. For most ATMPs, respondents indicated that no alternative treatment was available at all, that all other treatment options had been exhausted (i.e., lack of alternative treatment) (n = 6/12) or that there was an urgent, time-limited need for ATMP treatment (i.e., clinical urgency to treat) (n = 4/12). Other reasons included ensuring continued availability after the implementation of the ATMP Regulation (n = 1/12) or enabling treatment for a low number of patients (n = 1/12). Similar to HE, manufacturing under NPU was mainly motivated by clinical needs, largely due to a clinical urgency to treat (Table 2).

From the survey respondents, we interviewed 10 public facilities located in Belgium, Finland, Germany, Italy, the Netherlands and the UK. Public facilities that participated in interviews manufactured 17 ATMPs under exemption pathways (HE n = 7, NPU n = 10) (Figure 1). For each manufactured ATMP, a combination of reasons was given to motivate manufacturing under exemption pathways. First, clinical needs (lack of alternative treatment, clinical urgency to treat; for definitions, see Table S2) were consistently described as the main reason to motivate manufacturing under both HE and NPU pathways (as indicated in the survey). Respondents emphasized that ATMPs were used as a treatment of last resort. For instance, patients who suffered from graft-versus-host disease but did not respond to steroid treatment were treated with MSCs manufactured under HE. Patients who suffered from an acute, life-threatening infection, such as Epstein-Barr virus or cytomegalovirus, and did not respond to antiviral treatment were treated with virus-targeting lymphocytes manufactured under NPU. Furthermore, these clinical needs were described as occurring in situations in which treatment in a clinical trial was not possible because patients did not adhere to the inclusion criteria of ongoing trials or because trials were not ongoing when treatment was needed (Figure 1, Table S2).

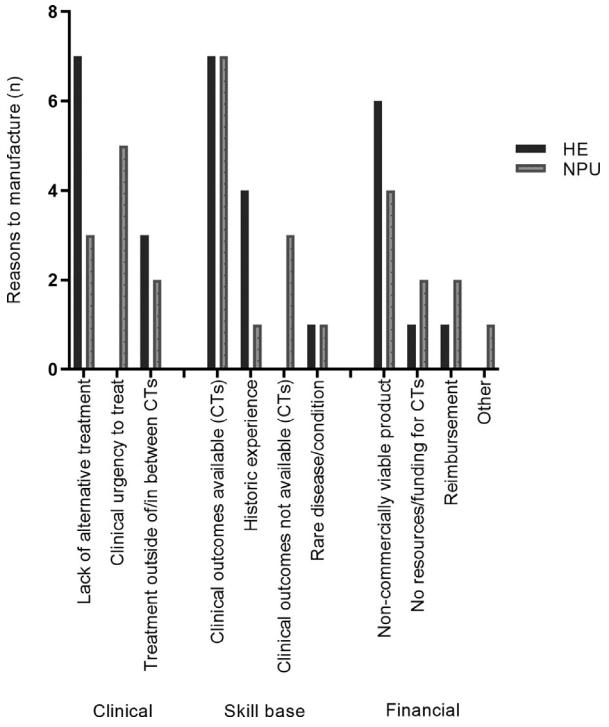

Fig. 1. Motivation for public facilities to manufacture ATMPs under exemption pathways (product-specific), stratified by reasons and exemption pathway. Multiple reasons per ATMP were described to motivate manufacturing under HE or NPU, including reasons within the clinical, skill base and financial categories. Only product reasons that were mentioned for more than one product were depicted. See Table S2 for full description of reason subcategories and categories. CT, clinical trial.

In combination with clinical needs, facilities gave reasons that motivated manufacturing under HE that related to clinical skill base and expertise on a product; for all ATMPs that were manufactured under HE, early clinical trials had been conducted or historic experience in clinical practice had been gained when the ATMP was available in the past as human cells or tissue. For one ATMP, the targeted rare disease or condition and the small patient population motivated the use of HE for manufacturing. With respect to financial aspects, it was indicated that most ATMPs were not considered commercially viable (e.g., due to a lack of interest by industry to pick up late clinical development) and were therefore manufactured under HE. For one ATMP, it was indicated that resources for continued in-house commercial development were lacking. By contrast, the manufacture of one ATMP under HE was financed through reimbursement. Similar reasons were given for motivating manufacture under NPU (Figure 1). Other reasons are included in Table S2.

Of the 10 interviewed facilities, three manufactured ATMPs under HE and three manufactured ATMPs under NPU. Four facilities did not manufacture ATMPs under exemption pathways (only for clinical trials). Facilities gave non-product-specific reasons that either motivated manufacturing under exemptions pathways, or motivated not manufacturing under exemption pathways. Facilities located in Finland, Italy, the Netherlands and the UK reported reasons to motivate manufacture under exemption pathways. They also reported complying with HE or NPU regulatory provisions as well as Good Manufacturing Practice (GMP). Short timelines for HE application procedures in Italy and the Netherlands facilitated manufacture under HE. Few financial aspects that were not directly related to a product were described as motivating manufacture under exemption pathways. Two facilities indicated that they applied for an HE license to support funding opportunities to conduct clinical trials through

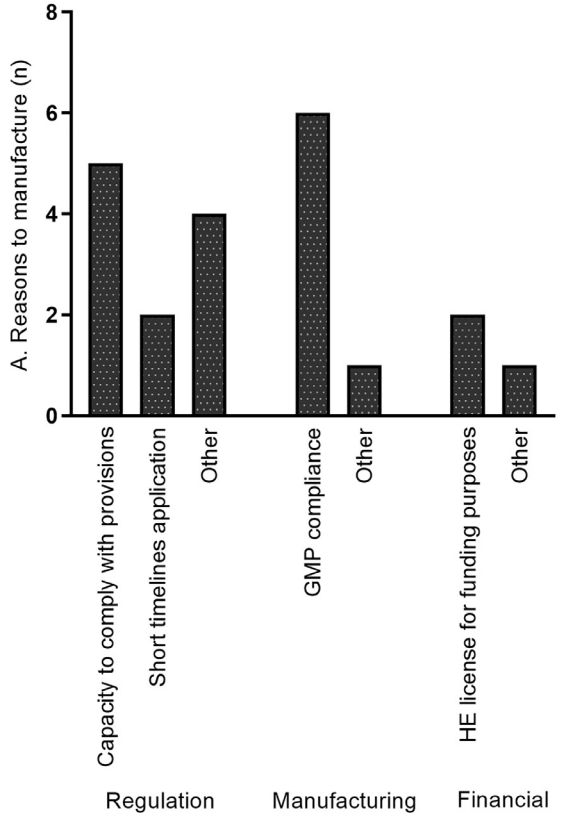

Fig. 2. Motivation for public facilities to manufacture (A) or to not manufacture (B) ATMPs under exemption pathways (non-product-specific), stratified by reasons. Only non-product reasons mentioned by more than one facility are depicted. See Tables S3–4 for full description of reason subcategories and categories.

grants instead of ATMP manufacturing under HE (Figure 2A). Details and other non-product-specific reasons for manufacturing under exemption pathways are provided in Table S3.

By contrast, facilities located in Belgium indicated that stringent provisions (mainly for clinical data), long timelines for HE applications and non-compliance with full GMP (e.g., qualified person release) were reasons not to manufacture under HE. Other frequently mentioned reasons to not manufacture under exemption pathways included high costs of manufacturing and payment from hospital budgets. Facilities indicated that possibilities for reimbursement and other funding options for manufacturing under HE in case of no reimbursement are limited (Figure 2B). Details and other non-product-specific reasons to not manufacture under exemption pathways are provided in Table S4.

Private ATMP manufacturing under HE

We identified nine private facilities that are HE license holders in two selected countries: six in Germany [26] and three in the Netherlands. We interviewed two private facilities in Germany that manufactured three ATMPs under HE between 2009 and 2017. One private facility in the Netherlands indicated that their HE license was inherited from an acquired facility and was not used for manufacturing. Results from interviews show that three ATMPs were manufactured by two private German facilities. These three ATMPs were autologous chondrocyte products for musculoskeletal disorders. For one ATMP, the scale of manufacturing and patient treatment was over 200 batches and patients between 2009 and 2017; for the other two ATMPs, the scale was unknown (not shown). The patient exposure ranged from a minimum of 202 to a maximum of 1500 under HE. Information in the public domain showed that four other private facilities in Germany are licensed to manufacture ATMPs—consisting of chondrocytes, MSCs, skin cells and hematopoietic stem cells—under HE. However, no other information, including the targeted indication [26], is provided. Details on the ATMP manufacturing activities of two other private facilities licensed under HE in the Netherlands are not available in the public domain.

The motivation to manufacture under HE by German private facilities included reasons related to historic product availability on the market and changing regulations. When the ATMP Regulation was issued, pre-existing German tissue product manufacturing licenses were transferred to HE licenses over time. Under German law, tissues are regulated as medicinal products and manufacturing needs to be GMP compliant [18]. Private facilities had capacity to comply with provisions for clinical data, and HE licenses were issued to continue their operations after the implementation of the ATMP Regulation. Financial reasons motivating manufacture under HE included reimbursement and generation of revenue from HE product sales to conduct large clinical trials. Institutional interests included interest in commercial development and centralized authorization in the EU.

Discussion

This study aimed to substantiate debates on HE by investigating product characteristics, scale and motivation for ATMP manufacturing under exemption pathways by public and private facilities. Results show that a modest number of ATMPs (n = 12) were manufactured under HE by public facilities. Most ATMPs consisted of mesenchymal stromal cells and targeted diseases or conditions within immunological diseases and hematology/oncology. The scale of manufacturing and patient treatment generally did not exceed 50 batches or treated patients per ATMP between 2009 and 2017. However, three ATMPs were manufactured and used for patient treatment on a relatively large scale by public facilities in Germany and the Netherlands. The total patient exposure to the ATMPs captured in the survey (40% response rate) ranged between 336 and 1600 under HE. The manufacture of ATMPs under HE was primarily motivated by clinical needs and clinical experience when treatment within clinical trials (either ongoing or future trials) was not possible. Regulatory aspects were described as motivating (Finland, Italy, the Netherlands) or limiting (Belgium, Germany) manufacture under HE by public facilities, depending on national procedures and in-house capacities. Financial resources often limited manufacture under HE by public facilities. In most selected countries, the manufacture of ATMPs under NPU was comparable to that under HE by public facilities. The scale of manufacturing and patient treatment was generally modest (up to 50 batches or treated patients) between 2015 and 2017. In the UK, NPU manufacturing (i.e., specials scheme) occurred on a relatively large scale compared with other countries. The total patient exposure to the ATMPs captured in the survey (40% response rate) ranged between 87 and 1400 under NPU. Similar to HE, the manufacture of ATMPs under NPU was primarily motivated by clinical needs. Overall, public facilities (excluding Germany) used HE in a compassionate use manner [18] to provide treatment for patients with clinical needs or as a tool to mitigate commercial development challenges. In Germany, ATMPs were manufactured for the national market under HE by several private facilities. The total patient exposure to the ATMPs that were manufactured by private facilities and captured in interviews ranged between 202 and 1500 under HE (2009–2017).

With the enactment of the ATMP Regulation, definitions of what would be considered an ATMP and therefore a medicinal product now included numerous human cell and tissue therapies that were historically used in hospital settings outside of medicinal product legislation (i.e., 'transition' ATMPs) [14]. Most manufactured ATMPs under HE were MSC products, and the reasons and situations in which public facilities used HE are indicative of the close proximity of

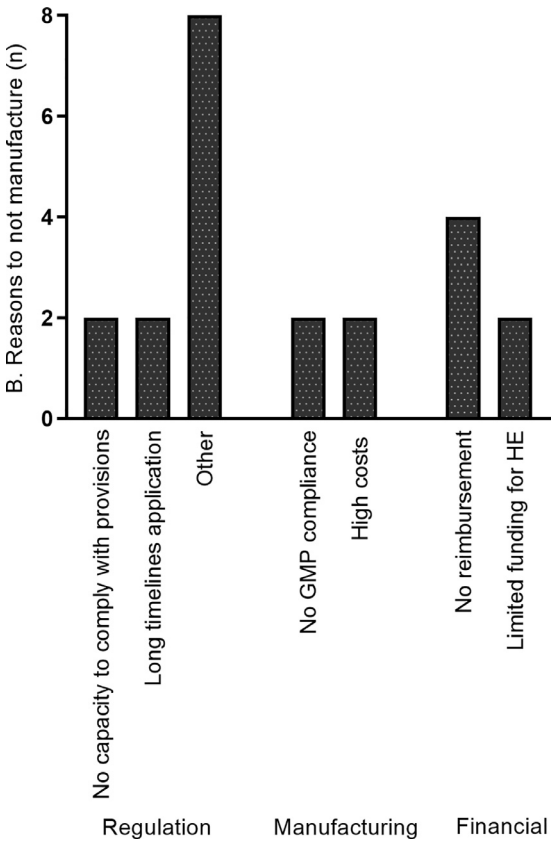

Fig. 2 Continued.

manufactured ATMPs to clinical practice. The manufacture of ATMPs was primarily motivated by clinical needs, they were used as a treatment of last resort, and product experience was gained historically in clinical practice or in clinical trials. Furthermore, ATMPs were manufactured for patients who could not be treated in ongoing clinical trials (because of non-adherence to inclusion criteria), or the ATMPs were not considered suitable for commercial development because of financial limitations in conducting late-phase clinical trials or a lack of interest on the part of commercial parties in continuing development. Thus, our results demonstrate that HE has been used to support the availability of ATMPs with close proximity to clinical practice and has played a critical role in enabling treatment for patients with clinical needs [8,21,22].

HE resembles the NPU pathway because both enable manufacturing to treat individual patients under the responsibility of health care professionals. The differences are that (i) HE is a specific pathway for ATMPs only, while NPU is a pathway for all medicinal products; (ii) HE provisions entail more requirements in comparison to NPU, particularly in countries that mandate clinical data for HE [18]; (iii) HE licenses require more prospective planning through more elaborate application procedures compared with NPU; and (iv) one HE license can be used for multiple patients, whereas applications for NPU are typically per patient [17,18]. The final difference insinuates that NPU manufacturing is used on a more ad hoc basis compared with HE, but both are used to treat few patients with custom-made ATMPs in selected countries. Yet under the specials scheme in the UK, manufacturing facilities obtain a license to manufacture a particular class of ATMPs, such as sCTMPs. Thus, specials licenses enable the manufacture of ATMPs in situations similar to those seen with HE in other countries (except Germany) [18]. However, regulatory provisions for a specials license and NPU in general are focused on manufacturing and quality [17,30], which indicates less centralized oversight on clinical safety and benefits under NPU in comparison to HE. Moreover, the differences among national NPU and CU pathways with respect to scope and eligibility, plus the ample space for multiple interpretations and difficulties distinguishing between NPU and CU pathways [17], indicate a need for a comparative analysis of regulatory procedures and requirements for approval under national NPU and CU pathways throughout the EU to mitigate lack of regulatory clarity for ATMP manufacturers.

Public stakeholders feared that the implementation of the ATMP Regulation could impair availability of ATMPs in clinical practice [8,23]. The environment of public facilities is centered around treatment and innovation in clinical practice and is different from pharmaceutical commercialization [31]. A previous study showed indications of limited institutional readiness [32,33] of hospitals and other public institutes to switch from point-of-care settings or human cells and tissue regulations to HE provisions [18]. Judged on previous reported numbers of HE license holders, limited capacity to comply is more prominent in countries with the most stringent quality and clinical data requirements for HE manufacturing, such as Belgium and Spain [18]. Furthermore, the regulatory reasons to not use HE for ATMP manufacturing shown here indicate that hospitals may struggle with GMP compliance, which requires substantial financial and human capital [14]. Yet reported hurdles for HE manufacturing extend well beyond regulatory and manufacturing challenges. Financial resources to manufacture ATMPs under HE have proven to be limited, similar to marketed ATMPs [20,32,34,35]. Without feasible regulatory provisions and sufficient financial resources, the use of HE to manufacture ATMPs with close proximity to clinical practice could be limited or even impaired in some countries. Central coordinating bodies for public facilities can strengthen collective technological know-how and reduce manufacturing and logistical costs [13], which in turn may improve opportunities for financial support. However, reimbursement is unlikely for products manufactured under HE with an uncertain benefit/risk balance. Stakeholders are exploring financial models for hospital products, such as conditional financing [36].

One of the main arguments against HE is that it could undermine commercial ATMP development by central EU authorization [9,37–40]. Our results indicate that the tension between manufacturing under HE by public facilities and commercial development is currently rather limited and that the pathways are more complementary than overlapping. Many ATMPs were manufactured under HE on a scale similar to that seen in early clinical trials, and the number of ATMPs manufactured under HE is modest compared with the vast number of clinical trials sponsored by academic centers in the EU [12]. Furthermore, the scale of HE versus NPU manufacturing was similar for most ATMPs (maximum 50 batches). Thus, considering the larger period of analysis for HE (9 years) versus NPU (3 years) manufacturing, the scale of manufacturing under HE is rather limited. In addition, many marketed ATMPs are gene- or cell-based products with different active substances compared with HE ATMPs. There is overlap between some publicly manufactured ATMPs under HE and marketed ATMPs for the therapeutic areas of immunological diseases and hematology/oncology, although the exact indications are different [41]. UK authorities have legislative power against potential competition of the specials scheme with marketed medicinal products (including pharmaceuticals and ATMPs) [30], and some but not all competent authorities of selected countries restrict HE manufacturing when alternative marketed medicinal products are available. A lack of legislative power against potential competition could create tension between manufacturing under HE by public facilities and commercial development (e.g., Germany, Spain) [18]. As scientific and technological advances progress and more public facilities are able to adopt ATMPs in clinical practice, this tension could increase over time.

By contrast, HE creates a competitive advantage for German companies in comparison to companies that are located in other EU

countries and bound to different HE provisions and utilization [18]. The HE licenses discussed here were critical to continuing operations after the ATMP Regulation was implemented for 'transition' tissue engineered products [42], and the HE licenses were regarded as temporary until central authorization was reached. However, not all German HE licenses were granted for 'transition' tissue engineered products; some concern relatively new ATMPs [26]. Furthermore, HE represents a national authorization for use, and it provides access to the German market and can be used as a stepping stone toward central EU authorization [18]. It represents a unique situation in comparison to the other selected countries, where more restrictive provisions limit manufacturing under HE to treatments of last resort or to public facilities, which reduces incentives for manufacturing under HE relative to commercial ATMP development [18]. The manufacture of chondrocytes under HE in Germany also contributed to withdrawal of a marketed ATMP in the past, so although patients may benefit from more available ATMPs under HE in Germany, patient access in other countries could be impaired because of EU market failure [43].

Competent authorities currently assess whether the scale of manufacturing is small and suitable for an HE license, among other provisions [18]; however, whether the ATMP is not commercially viable is not assessed. Some ATMPs are unsuitable for commercial development in the EU [22]—for instance, ATMPs that target multiple rare indications and other ATMPs with low commercial value and a high risk profile for commercial development [13,22]. As a result, ATMPs with positive clinical outcomes are at risk of getting stuck in early clinical development [13] or disappearing without manufacturing under HE. Therefore, it is paramount to go beyond criteria of scale for HE and to assess whether ATMPs are not commercially viable—for instance, when opportunities for intellectual property protection and reimbursement are limited [44]. Other ATMPs with high commercial value and acceptable risk profiles are better suited to being transferred to industry or developed in public-private partnerships [13,45]. This would facilitate use of the HE pathway to meet clinical needs when the market fails, while commercially viable ATMPs are developed further for centralized marketing authorization. Yet criteria to determine whether ATMPs are not commercially viable are likely to be a moving target as a result of scientific and technological advances and changing commercial opportunities and to require a continuous, open dialogue between the European Commission, competent authorities and public and private stakeholders in the field.

Our results are a first step toward insight into product characteristics, scale and motivation for ATMP manufacturing under HE in selected EU countries. Data on HE in selected countries are nearly complete, except for France and Germany, judging by earlier reported numbers of HE license holders [18]. The response rate to the study survey (40%) mainly leads to missing NPU data and to missing HE data of potentially one or two public facilities in Finland, Italy and the UK. Yet out of the nine initially selected EU countries, we did not reach public HE license holders in France or private HE license holders in Germany [18]. Public sources are available for these HE licenses in France and Germany; however, they do not provide detailed information on product characteristics [25,26]. These limitations underline the lack of transparency on ATMP manufacturing activities under exemptions throughout the EU. A multi-stakeholder mandate for EU-wide public registries is encouraged to enhance transparency on HE manufacturing [40]. A registry with product and facility information for all ATMPs manufactured under HE in the EU could facilitate coordination between public facilities and inform business opportunities and market access planning for industry [43]. In addition, EU-wide registries for clinical outcomes could increase the knowledge base and facilitate informed decision-making for the care of individual patients and public health. Currently, clinical outcomes of treatment under HE need to be reported to the competent authorities through annual reporting [18], but these are not available in central EU-wide registries. Furthermore, there are no regulatory requirements for long-term follow-up through registries under HE, while registries are often imposed for marketed products as post-marketing requirements upon marketing authorization [46]. How ATMPs manufactured under HE can be optimally grouped in registries for clinical outcomes—for example, by therapeutic indication or type of clinical outcome measure—needs to be determined.

In conclusion, manufacturing under HE by public facilities supports the availability of ATMPs with close proximity to clinical practice for patients in need. However, in some countries HE provisions limit utilization of the pathway, whereas in others private HE licenses undermine commercial developments that go through the centralized procedure. Guidance to distinguish between ATMPs that are or are not commercially viable, transparency through a public EU-wide registry on HE manufacturing and collaboration between public facilities and commercial developers are needed to optimize the use of both HE and regulatory pathways for commercial development.

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Declaration of competing interest

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Author contributions

Conception and design of the study: DC, JH, MB, IS-C, HL, PM, HG. Acquisition of data: DC, PM, IS-C. Analysis and interpretation of data: DC, JH, HG. Drafting or revising the manuscript: DC, JH, MB, IS-C, HL, PM, HG. Supervision: JH, MB, HL, PM, HG. All authors have approved the final article.

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Supplementary materials

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