Research Article

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Regulating advanced therapy medicinal products through the Hospital Exemption: an analysis of regulatory approaches in nine EU countries

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Aim: To study regulatory approaches for the implementation and utilization of the Hospital Exemption (HE) in nine EU countries. **Materials & methods:** Using public regulatory documentation and interviews with authorities we characterized the national implementation process of the HE, including national implementation characteristics and two outcomes: national licensing provisions and the amount of license holders. **Results:** National licensing provisions vary substantially among selected countries as a result of different regulatory considerations that relate to unmet medical needs, benefit/risk balance, and innovation. The amount of license holders per country is moderate (0–11). **Conclusion:** The HE facilitates HE utilization in clinical practice in some countries, yet safeguarding of public health and incentivizing commercial development is challenging.

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Keywords: advanced therapy medicinal product • clinical practice • commercial development • drug regulatory science • hospital exemption • implementation process • license holders • national licensing provisions

Gene and cell-based therapies (GCTs) represent a challenging class of therapies to appropriately accommodate into the regulatory framework for marketing authorization of pharmaceuticals (i.e., small molecules and biologics). Inherent product characteristics such as the complexities of scaling-up manufacturing and working with and transporting tissues and cells, impose developmental and regulatory challenges on quality aspects and manufacturing procedures [1,2]. Furthermore, as many GCTs originate from academic centers and have close proximity to clinical practice, there are questions about how pre-existing regulatory requirements for ensuring safety and efficacy of the medicinal products produced can be fulfilled in GCT development close to clinical practice [3–5]. Authorities around the world responded by introducing flexibilities for GCTs in existing licensing regimes for medicinal products [6–8]. In the EU and Japan, authorities also exempted some GCTs from medicinal product regulations altogether to accommodate noncommercial activities [9,10].

EU policy makers harmonized GCT regulations across member states by implementing the Advanced Therapy Medicinal Product (ATMP) Regulation (1394/2007) in 2009 after multiple public consultations [11]. Motivated to protect public health and ensure patient safety [1], the ATMP Regulation subjects GCTs to the centralized authorization procedure of the EMA, making it mandatory that GCTs are developed based on stringent evidentiary requirements of evidence-based medicine and multiple stages of clinical trials [12]. Definitions of ATMPs, and therefore medicinal products, include therapies that have been historically used in hospital settings and regulated human tissues and cells [13]. Yet, the ATMP Regulation only applies to ATMPs that are industrially prepared and

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intended for the market [9,14]. The draft proposal for the ATMP Regulation stated that noncommercial activities were exempted from the centralized ATMP regulations [14], and initial statements were redrafted into Article 28 of the final ATMP Regulation, the so-called Hospital Exemption (HE).

The HE allows manufacturing of ATMPs that are "*processed on a non-routine basis according to specific quality standards, and used within the same EU member state in a hospital setting 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*" (Regulation European Commission [EC] 1394/2007, Article 28). Implementation of the HE was left to individual member states and their national competent authorities [9]. Previous studies reported that difficulties in how to interpret the terminology of Article 28 (e.g., 'non-routine') led to divergent national regulatory approaches for the HE and transposition delays [10,15,16]. For instance, French, Italian, Lithuanian, Polish, Spanish and United Kingdom (UK) provisions lack clear definitions related to 'non-routine' [17,18]. French and UK entry provisions differ due to national existing legislation [17], and provisions for data requirements range from quality (e.g., Finland [FI]) to quality, nonclinical and clinical data (e.g., Spain [ES]) [15]. Furthermore, several factors are reported to be instrumental in how Article 28 was implemented, which include external influence from industry on the implementation process in France (FR), Germany (DE) and the UK [15], existing regulations for tissue products in DE [19] and the availability of other national exemption pathways such as the Specials scheme in the UK [20]. Previous work also shows that HE utilization occurred in DE and the Netherlands (NL), among others [21,22]. Yet, how regulatory licensing provisions and HE utilization compare among various EU countries is largely unclear.

In this study we provide a comparative analysis of how competent authorities across multiple EU countries interpreted Article 28 and implemented the HE nationally. We compare two outcomes of the implementation process; national licensing provisions and the amount of HE license holders across countries. Additionally, we shed light on how characteristics of the implementation process of the HE, including role divisions between competent authorities, discussions on intended purpose for the HE and capacities of developers, are associated with outcomes. The comparative analysis includes nine countries (Austria [AT], Belgium [BE], FI, FR, DE, Italy [IT], NL, ES and UK). It provides clarity on variation in HE implementation, informs the debate on the HE within the wider debate of regulatory change for ATMPs, and facilitates policy learning for HE utilization across EU countries.

Materials & methods

Country selection

We selected European countries with the following attributes: a member state of the EU, implemented provisions by June 2018 and showed indications of ATMP clinical activity, either evident through the conduct of clinical trials [5] and/or ATMP manufacturing under the HE [21]. We ensured to include countries from various European regions. Based on these criteria, we selected AT, BE, FI, FR, DE, IT, NL, ES and the UK.

Analytical framework

Article 28 is listed as an amendment to the overarching Directive 2001/83/EC for medicinal products, and therefore, is required to be transposed into national law by each EU member state [23]. Through transposition into national law, competent authorities of member states are made responsible for drafting specific national licensing provisions and putting these into use on a national level. When national licensing provisions are implemented, the authorization of HE licenses is put under the authority of either the national regulatory authority or the inspectorate.

Based on previous work [23,24], an analytical framework was developed to understand the implementation process in each selected country. The implementation process was separated into a transposition phase defined as the process of translating Article 28 into national provisions for the HE and a utilization phase defined as putting national provisions into practical use. Utilization starts from the moment applications for a HE license can be submitted (Figure 1).

The framework distinguishes between the process of regulatory implementation and outcomes of the transposition phase and utilization phase. We defined the national licensing provisions for the HE as the outcome of the transposition phase and the authorization of HE licenses (yes/no) as the outcome of the HE utilization phase. The latter was further substantiated as the number of license holders per country (Figure 1). Outcomes were captured between May and October 2018.

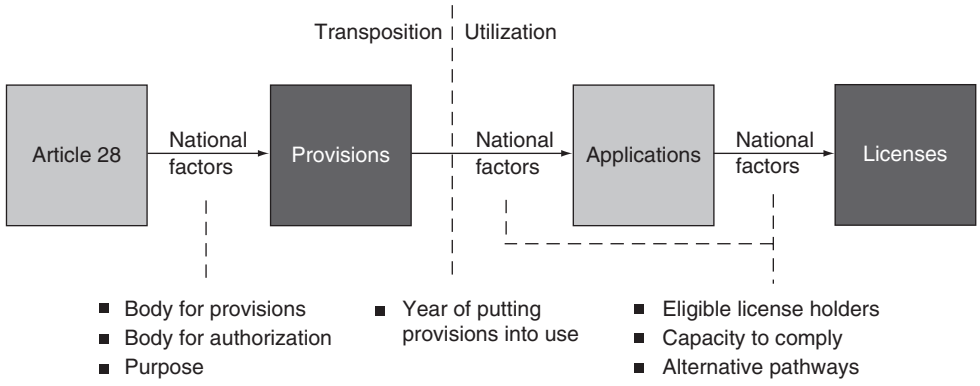

Figure 1. Schematic chronological representation of the Hospital Exemption implementation process.

Data collection

Regulatory documentation

The websites of the competent authorities of the selected countries were used to search for information on national licensing provisions for the HE [25–33]. We defined national licensing provisions as all legislative regulations, guidance documents and procedural forms, including law, royal decrees, regulations, guidelines and application forms. If information on provisions was not available in English or Dutch, Google Translate was used to translate documentation from other languages into English. Documents were investigated in May–August 2018. If multiple versions of documentation (e.g., guidelines and application forms) were available, the most recent version was used for analysis.

Interviews

Invitations for interviews were sent to senior employees of the inspectorate and national regulatory authorities per selected country. The most suitable interviewee for the interview within the main responsible body for the HE was identified through email contact. We conducted nine interviews in total, with one (AT, BE, FI, DE, ES and UK), and three (NL) ATMP experts of the competent authorities, respectively. The competent authorities of FR and IT were unavailable for interviews. All interviewees were senior ATMP experts within their national regulatory agency for medicinal products and had first-hand experience or knowledge on the implementation process and HE authorizations.

A semi-structured interview guide was used (Supplementary Material 1) to discuss and verify national provisions for the HE (outcome of transposition phase) and HE utilization (outcome of utilization phase), as well as to discuss how national characteristics of the implementation process contributed to these outcomes from a regulatory perspective by asking questions on the transposition process, the context in which provisions emerged and on utilization (Supplementary Material 1). Oral consent for recording was sought before interviews were started, and anonymity was ensured to the interviewees. Interviews were conducted between June and October 2018, and fully transcribed. Reported information in this study was verified with the interviewees in July 2019.

Data analysis

National licensing provisions

The national licensing provisions laid out in regulatory documentation were grouped into four main categories: scope, eligibility criteria, data entry requirements and process standards (Supplementary Table 1). Each provision category was assessed on a number of specific aspects that were defined based on previous work [34] and knowledge of the design and functioning of regulatory pathways. Assessment was first done based on regulatory documentation and then verified using information from the interviews. To compare provisions across countries, we distinguished between: provisions that are the same in each country and directly originate from Article 28 (e.g., process standards for manufacturing); provisions that varied among countries, but still originated from Article 28 (e.g., 'preparation on a non-routine basis' and 'preparation of custom-made products for individual patients'); and additional provisions that differed among countries and did not directly originate from Article 28 (e.g., data entry requirements).

Table 1. Article 28 provisions.

Category	Provision
Scope	Nonroutine processing Custom-made product for individual patient
Eligibility	Delivery on individual medical prescription Treatment in hospital No export
Data entry requirements	Nondefined
Process standards	National traceability regulations National pharmacovigilance regulations Manufacturing & quality equivalent to ATMP authorization pathway (regulation 1394/2007)

ATMP: Advanced therapy medicinal product.

HE license holders

Data on regulatory experience with HE licensing were captured in terms of whether applications for HE licenses were filed (yes/no), and amount of authorizations of HE licenses, extracted from the transcripts, tabulated and comparatively analyzed among countries. Additionally, we searched for online regulatory information on HE license holders for all countries to supplement information from the interview transcripts.

National characteristics of the implementation process

National characteristics that played a role in the process of transposition and utilization were qualitatively analyzed in NVivo Pro v11 to shed light on how national variation in implementation contributed to outcomes. We identified national characteristics of the implementation process described in the interview transcripts through an initial round of open coding and grouping of codes (Supplementary Table 2). The coding round revealed the importance of national characteristics on outcomes, and substantial variability among countries. Some characteristics correspond with previously reported characteristics in literature (e.g., existing legislation, external influence, year of implementation and other exemption pathways) [15,16,19], yet, others were grouped entirely in an inductive manner (e.g., intended purpose).

Due to the large variability of identified implementation process characteristics, we performed an axial round of coding to identify characteristics that were commonly described by all competent authorities in relation to the studied outcomes. Three characteristics of the implementation process were frequently mentioned in relation to national provisions: the body for drafting the provisions, the body for HE authorization within the national competent authority and the intended regulatory purpose of the HE. Three characteristics were frequently mentioned in relation to the outcome of HE authorization: the eligible license holders, their capacity to comply with national licensing provisions and the availability and preference to manufacture noncentrally licensed ATMPs under alternative pathways. The characteristics and their values per country were extracted from NVivo in order to perform a comparative analysis of characteristics of the implementation process and their association with studied outcomes among countries.

Results

National licensing provisions for the HE

National licensing provisions for the HE vary among selected EU countries. We distinguish between provisions originating from Article 28 that are the same in each country, provisions originating from Article 28 that vary among countries and additional provisions not originating from Article 28 that vary among countries.

Nonvariable provisions

Article 28 imposes some licensing provisions for the HE that are fully transposed into national provisions and implemented in the same way across the studied countries. These provisions entail ATMP manufacture by delivery on prescription, for treatment of individual patients in hospitals under the responsibility of medical practitioners, no export of manufactured ATMPs, and compliance with quality requirements for ATMPs equivalent to centralized authorization pathways and national regulations for traceability and pharmacovigilance (Table 1). All selected countries fully transposed these Article 28 provisions into national provisions, except for FR. For nonpharmaceutical establishments in FR, adherence to GMP guidance suffices in order for these establishments to meet GMP

requirements over time. In all other selected countries, compliance with GMP regulations is mandatory. Extensive manufacturing and quality data are mandatory in all selected countries to enter the HE pathway (Table 2). Furthermore, all countries incorporated national provisions for traceability and pharmacovigilance that are similar to regulations for pharmaceuticals (not shown).

Variable provisions

Other provisions showed more variability on a national level (Table 2). Some Article 28 provisions were not transposed into clearly defined provisions in all selected countries in particular for 'preparation on a non-routine basis' and 'preparation of custom-made products for individual patients'. Five countries (BE, NL, FI, DE and UK, and not AT, FR, IT and ES) provide guidance in their provisions to what could be considered 'preparation on a non-routine basis'. These revolve around manufacturing on a scale similar to first-in-man trials (BE), small scale manufacturing for few patients (NL), nonindustrial manufacturing (FI), products for which a full benefit/risk evaluation under commercial trajectories is not possible (DE) and scale of manufacturing in comparison with other manufacturing activities (UK). There were no defined limitations on the number of patients that can be treated under a HE license, except in NL (ten patients per year, or a maximum of 50 patients per year for renewed licenses). Yet, all interviewees indicated that 'non-routine' was interpreted as ATMP manufacturing for treatment on a small scale in hospitals, which is evaluated on a case-by-case basis. Whether ATMP manufacturing under a HE license remains within the scope of 'non-routine' is re-evaluated over time based on mandatory annual reporting that includes scale of manufacturing and patient treatment in all selected countries (Table 2). None of the authorities described revoking HE licenses due to large-scale manufacturing.

Additional provisions

Article 28 was supplemented with additional provisions in all countries, except for the UK. Across countries, several provisions in various combinations were described that are part of assessment procedures and relate to: whether clinical evidence is required for a HE license, the type of eligible license holders (hospitals/public, unrestricted), restrictions when alternative treatment for the same indication (licensed pharmaceuticals, including but not limited to ATMPs) is available to prevent competition and whether manufacturing under a HE is required to target an unmet medical need (Figure 2).

BE, DE, NL and ES have stringent clinical data entry provisions for the HE. All available clinical data are required in order for the authorities to perform a preliminary benefit/risk assessment. Assessment for licensing follows similar principles to benefit/risk assessments in other authorization pathways. However, less robust data can suffice to assess benefits and safety for patients, based on case-by-case considerations. In NL, established safety suffices for authorization. On top of these clinical data provisions, the product should target an unmet medical need and restrictions are in place when licensed pharmaceuticals are available in BE and NL. In ES, only hospitals are eligible to apply for a HE license. German provisions have stringent clinical data entry provisions, but do not impose further restrictions (Figure 2).

There are five countries where HE licenses can be granted without clinical evidence: AT, Fl, FR, IT and the UK. Clinical data can be submitted if available. However, other additional provisions were implemented to restrict the use of the HE. In FR, HE license applications without clinical data need to target an unmet medical need and no other licensed pharmaceuticals should be available. Targeting unmet medical need is required for licensing in AT, Fl and IT as well. In Fl and IT, licensing is further restricted when other licensed pharmaceuticals are already available (regardless of clinical data availability). At last, HE licenses are only granted to hospitals and public institutes in AT and IT, respectively. The UK is the only selected country where HE licenses can be granted without clinical evidence and without additional provisions (Figure 2).

HE license holders

Whether HE authorizations were granted and the amount of HE license holders varied between the selected countries as of June 2018. The number of HE license holders was relatively high in FR [35], DE [36] and NL (Table 3). In FR, there are 11 public facilities that hold one or two types of HE licenses (HE authorization under a national product authorization, and/or under a clinical trial framework) to manufacture HE products [35]. There were seven HE license holders in DE, of which most were companies (n = 6). There was one company that holds two HE licenses [36]. In NL, the number of HE license holders was relatively large (n = 11), of which most were academic hospitals and public facilities (n = 7). Dutch license holders may hold several licenses for individual

Table 2. Variable and additional national provisions for the Hospital Exemption, per selected country.

	AT	BE	FI	FR	DE	IT	NL	ES	UK
Scope									
Nonroutine/custom-made product	Nondefined	Guidance	Guidance	Nondefined	Guidance	Nondefined	Guidance	Nondefined	Guidance
Number of patients	Nondefined	Nondefined	Nondefined	Nondefined	Nondefined	Nondefined	10/50 patients	Nondefined	Nondefined
Duration of license	Nondefined	1 year	Nondefined	5 years	Nondefined	Nondefined	1 year	3–5 years	Nondefined
Annual reporting	Required	Required	Required	Required	Required	Required	Required	Required	Required
Eligibility									
Eligible license holders	Hospitals	All	All	All	All	Public institutes	All	Hospitals	All
Restricted when licensed products are available	No	Yes	Yes	Yes[†]	No	Yes	Yes	No	No
Medical need considerations[‡]	Yes	Yes	Yes	Yes[†]	No	Yes	Yes	No	No
Data entry requirements									
Manufacturing & quality	Required	Required	Required	Required	Required	Required	Required	Required	Required
Clinical	Not required	Required	Not required	Not required	Required	Not required	Required	Required	Not required
Process standards									
GMP compliance	Required	Required	Required	Not required[§]	Required	Required	Required	Required	Required

[†]When clinical data are not available.
[‡]Refers to whether the competent authority considers medical need justifications in their decision making for authorization.
[§]Not required for non-pharmaceutical establishments only.
AT: Austria; BE: Belgium; DE: Germany; ES: Spain; FI: Finland; FR: France; IT: Italy; NL: Netherlands; UK: United Kingdom.

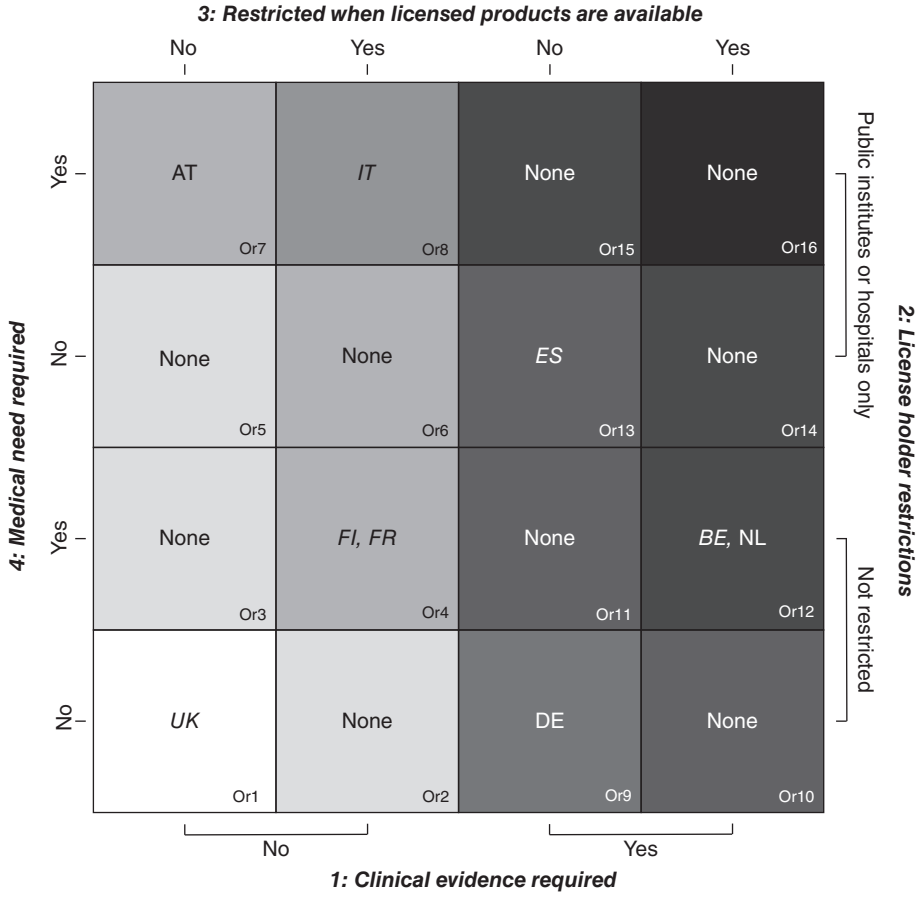

Figure 2. Additional provisions for the Hospital Exemption in selected countries. Shading from white (Or1) to black (Or16) depicts the increasing stringency of the combination of additional provisions. Or1 depicts no clinical data, no additional provisions; Or2,3,5 depicts no clinical data, one additional provision; Or4,6,7 depicts no clinical data, two additional provisions; Or8 depicts no clinical data, three additional provisions; Or9 depicts clinical data, no additional provisions; Or10,11,13 depicts clinical data, one additional provision; Or12,14,15 depicts clinical data, two additional provisions; and Or16 depicts clinical data, three additional provisions. Italic depicts detailed regulations (including decrees), no italic depicts Article 28 transposition into law combined with practical guidance.
AT: Austria; BE: Belgium; DE: Germany; ES: Spain; FI: Finland; FR: France; IT: Italy; NL: Netherlands; UK: United Kingdom.

Table 3. Hospital Exemption authorizations and applications in selected countries.

Country	Authorizations (n license holders)	Applications
Austria	No	No
Belgium	No	No
Finland	Yes (2)	Yes
France	Yes (11)	Yes
Germany	Yes (7)	Yes
Italy	Unknown†	Unknown†
Netherlands	Yes (11)	Yes
Spain	No	Yes
United Kingdom	Yes (1)	Yes

†Authorities were unavailable for interviews.

Table 4. Overview of national characteristics and outcomes of the implementation process.

Country	Transposition national factors			Outcome	Utilization national factors				Outcome
	Body for drafting provisions	Body for authorization	Purpose	Provisions†	Year of putting provisions to use	Eligible license holders	Capacity to comply	Alternative pathways	Amount of license holders‡
Austria	■	•	•	•	2017	•	□	■	○
Finland	◙	◙	•	•	2009	■	□	□	□
UK	■	•	•	○	2010	■	■	■	□
Belgium	□	□	□	■	2017	■	□	□	○
Netherlands	◙	◙	□	■	2010	■	■	□	■
Germany	■	□	■	□	2010	■	■	□	■
Spain	□	□	■	■	2014	•	□	■	○

†Reflects national provisions during May–October 2018.
‡Reflects Hospital Exemption license holders during Jun–Oct 2018.
Transposition: Body for drafting provisions: ◙ = Inspectorate in collaboration with regulatory authority, □ = Regulatory authority, ■ = Ministry in collaboration with regulatory authority and/or inspectorate; Body for authorization: • = Inspectorate, ◙ = Inspectorate in collaboration with regulatory authority, □ = Regulatory authority. Outcome: Purpose: • = Unmet medical needs, □ = Unmet medical needs and benefit and safety, ■ = Benefit and safety and innovation; Provisions: ○ = No clinical evidence required, no additional provisions, • = No clinical evidence required, with additional provisions, □ = Clinical evidence required, without additional provisions, ■ = Clinical evidence required, with additional provisions.
Utilization: Year of putting provisions to use: (year); Eligible license holders: • = Hospitals only, ■ = Not restricted; Capacity to comply (with provisions): □ = Limited capacity, ■ = Capacity by eligible license holders; Alternative pathways (regulatory pathways for noncentrally licensed products): □ = No alternative pathways preferred or available, only other pathway is clinical trial, ■ = Use of alternative pathways; License holders: ○ = None, □ = Limited, ■ = Relatively high.

products per facility, which need to be renewed each year. There were relatively few HE license holders in Fl (n = 2, public) and the UK (n = 1, public). In ES, none of the HE applications had been authorized. In AT and BE no applications had been received by the authorities. Some authorities indicated few applications were under evaluation or expected in the near future. The number of authorizations in IT is unknown (Table 3).

National characteristics of the HE implementation process

The implementation process for the HE differed across countries. Interview respondents described national characteristics related to the process of transposition, alignment with existing national legislation and the perceived need for and capacity to comply with the HE by national manufacturers. Supplementary Table 2 provides a comparative overview of all characteristics described by interview respondents.

Interview respondents also described discussions on the kind of manufacturing activities that were deemed suitable for the HE from a regulatory perspective. Discussions on suitability led to an intended regulatory purpose for the HE in each country as perceived by the interviewees. The purpose was described as playing an imperative role in the drafting of national provisions. Across countries, several purposes were described in various combinations: to fulfill unmet medical needs, to provide treatment of sufficient benefit and safety (i.e., benefit/risk balance) and to collect data for central authorization (innovation pathway) (Table 4). The competent authorities of FR and IT were unavailable for interviews, and therefore, not described below.

Across countries, the intended purposes were different depending on the bodies that were responsible for the transposition and/or granting of licenses. When inspectorates were mainly involved in transposition and responsible for granting licenses, the purpose of the HE was focused on manufacturing for unmet medical needs (AT, FI and UK). In contrast, when regulatory authorities were involved in transposition and the drafting of licensing provisions, and/or when they were responsible for granting licenses, the purpose of the HE was also focused on treatments of sufficient benefit and safety (BE, DE, ES and NL) (Table 4). Furthermore, Article 28 was either transposed into national law with more detailed provisions in guidance documents, or national provisions were transposed into detailed national regulations (Figure 2). These variations illustrate that national political procedures for the transposition of EU legislation differ among countries. Importantly, similar purposes and provisions did not result in the same amount of HE license holders among countries. To allow for a comparative analysis, we group countries with common purposes and provisions, and describe their implementation process characteristics to shed light on differences in the amount of HE license holders among countries (Table 4, & Supplementary Table 2).

Unmet medical needs

In AT, Fl and UK, the HE was intended as a manufacturing license for therapies indicated to treat patients with unmet medical needs (Table 4). Not many additional licensing provisions were implemented (Figure 2), but the amount of license holders is low in all three countries. In AT, implementation occurred relatively late (2017). The lack of applications was further attributed to Austrian drug law, which allows ATMP manufacture in point-of-care settings without centralized oversight. Hospitals were also reported to have limited GMP manufacturing capacity. In Fl, the amount of HE license holders is limited, despite the possibility to manufacture ATMPs for human administration before clinical trial conduct. It was reported that some applications were withdrawn before GMP inspection. Furthermore, in both AT and Fl it was reported that most patients receive ATMP treatment within commercially sponsored clinical trials. In the UK, policy makers had concerns related to the ambiguous terminology in Article 28 and potential competition with licensed pharmaceuticals [37]. This created a general view that the historically used Named Patient Use pathway (i.e., Specials scheme) was better suited to manufacture unlicensed ATMPs for unmet medical needs (Table 4 & Supplementary Table 2). The amount of HE license holders is limited, while there are many public and private facilities that hold a Specials license for ATMP manufacture (~25) [38].

Unmet medical needs & benefit/risk balance

In BE and NL, the HE was intended as a manufacturing license for unmet medical needs when clinical trials or central authorization are not feasible (Table 4). The requirement to demonstrate a preliminary benefit/risk balance means that clinical evidence is required, and other additional provisions are similar (Figure 2). Yet, authorizations were granted in NL, but not in BE. The Dutch inspectorate implemented additional provisions through guidelines and procedures in close consultation with regulators and mostly public stakeholders in 2010. Patients without further treatment options can be treated with ATMPs manufactured under the HE if safety has been established. Capacity to comply with provisions was not considered to be a hurdle for authorization. In BE, regulators drafted a royal decree, which was implemented relatively late in 2017 after a lengthy consultation process. The lack of applications was attributed to stringent clinical data requirements, GMP and quality requirements that are equivalent to the centralized procedure, and a lack of capacity to comply (Table 4).

Benefit/risk balance & innovation

In DE and ES, the HE was intended as a national authorization when clinical trials or central authorization are not, or not yet, feasible, in order to enable patient access to beneficial and safe ATMPs, and stimulate innovation by allowing clinical data collection that can support dossiers for central authorization (Table 4). Provisions are relatively similar, except that license holders are restricted to hospitals in ES (Figure 2). Yet, authorizations were granted in DE, but not in ES. In DE, policy makers extended pharmaceutical regulations to HE provisions, considering that tissues and cells are also regulated as pharmaceuticals. Many applications were filed, but also rejected or withdrawn due to limited capacity to comply with provisions. In DE, HE licenses were granted to companies to manufacture ATMPs that were previously manufactured under tissue licenses, but also for a few new ATMPs. Data collection led to centralized marketing authorization of one HE product [36], which was enabled by German provisions: the HE can be used as a stepping-stone toward centralized authorization, companies are eligible and manufacturing under the HE is not restricted when alternative marketed medicinal products are available. In ES, regulators drafted a royal decree, which was implemented relatively late (2014). Applications were limited and none were authorized due to a lack of capacity to comply with provisions or due to ongoing assessment. Named Patient Use was reported to be used for ATMP manufacture (Table 4 & Supplementary Table 2).

Discussion

In this study we document how the HE has been implemented in various EU countries. Our results show that national licensing provisions vary substantially as a result of discretionary interpretation of Article 28. In some countries, national provisions resemble the basic Article 28 provisions to accommodate ATMP manufacturing for unmet medical needs. In other countries, additional provisions (e.g., clinical data requirements) led to HE pathways that shifted toward procedures for national authorization. Some countries implemented the HE as a stepping-stone for central authorization, while others put restrictions on the HE to prevent competition with licensed pharmaceuticals.

More restrictive provisions are expected to result in fewer HE license holders, but our results indicate otherwise. HE licenses were authorized to accommodate local manufacturing activities in hospital settings [14] in FR and NL,

and to some extent in Fl and the UK, which have varying levels of stringency in their licensing provisions. In DE, mainly companies hold HE licenses to manufacture ATMPs, as well as a few companies in NL. In AT, BE and ES, HE licenses were not granted yet. Limited utilization of the HE was often attributed to limited capacity to comply with provisions (mainly manufacturing, quality and clinical data requirements), implementation delays or to alternative pathways that are preferred over the HE pathway (e.g., UK's Specials scheme).

Transposition of EU legislation is a challenging process; delays are common and national opposition to EU directives may lead to deviations from the original policy [23]. For the HE, the ambiguous terminology and lack of a clearly defined purpose in Article 28 led to discretionary implementation of national provisions among selected countries, which has been a point of critique [10]. Harmonization of national provisions for the HE could provide more regulatory clarity and reduce variety as to how the HE is used among countries in the EU [39,40]. It might also facilitate utilization and availability in some countries that have limited utilization of HE so far. However, harmonization across countries is naturally less aligned with local activities and opportunities [12], and may be beneficial for some countries but not for others. The variety of national provisions of the HE and utilization in clinical practice underline differences in political choices and differences in national innovation system characteristics in terms of, for example, ATMP developers and biomedical knowledge base. From this perspective, national variation can be seen as an outcome of 'boundary work' by national member states to retain competencies and responsibilities at the national level in close alignment with their respective healthcare systems [17].

The regulatory flexibilities that are incorporated in the ATMP Regulation indicate that authorities are searching for justified flexibility from stringent requirements for medicinal product authorization under the centralized pathway, in an attempt to balance the protection of public health and ATMP development and innovation [9,41]. The tension between the need for potentially life-saving treatment and for benefit/risk data is stronger for the HE compared with centralized marketing authorization of ATMPs. Article 28 exempts ATMPs from evidentiary requirements for centralized authorization of ATMPs, with some exceptions such as GMP compliance. These subpar evidentiary requirements have been postulated to put patients at risk [42]. Due to the unmet medical need and scientific uncertainty that is so typical to the ATMP field [1,41], it becomes an ethical question to find the right balance between patient needs versus patient benefits and safety. In clinical practice, patients and healthcare professionals decide whether risks and uncertainties are acceptable considering the prognosis. Yet, authorities have a mandate gatekeeper function to protect patients and society from unacceptable risks [10,42], but also from malicious practices including treatment without benefits [43]. Considering that more comprehensive or confirmatory evidence of a benefit/risk balance, as is required for the centralized pathway, is not required under the HE in all selected countries, it appears justified to safeguard public health and patient safety through the implementation of additional provisions. This regulatory approach particularly suits ATMPs that have close proximity to practices with long clinical history and for which evidentiary support of clinical benefits and safety might already be available such as cultured tissue for severe burn wounds [13,44] or stem cell therapies [8]. Furthermore, it is important to make sure that there is a strong focus on learning while doing in the HE. Further collection of evidence can be achieved through provisions to protect patients and guarantee the monitoring of benefits and risks over a longer period of time (e.g., through registries for long-term follow-up), in particular when larger groups of patients are treated under the HE.

When the ATMP Regulation was implemented, it was feared that its stringent regulations would impair availability of ATMPs in clinical practice, in particular for noncommercial activities by public facilities [8,45,46]. Limited availability may be explained through the notion of institutional readiness to adopt new practices and structures in clinical practice [47,48]. In this study we found limited institutional readiness for the uptake of ATMPs in some countries. Therefore, competent authorities and stakeholders in the field are recommended to collaborate for capacity building for GMP manufacturing, pharmacovigilance, traceability, and quality and clinical data collection in order for eligible license holders to comply with HE provisions and to gear up for compliance with the wider principles of the ATMP Regulation. However, limited institutional readiness to switch from point-of-care settings or manufacturing under national human cells and tissue regulations to HE provisions, is likely dependent on the relative stringency of the HE provisions in comparison with clinical trial regulations and other factors that remain to be confirmed by public facilities. Enabling noncommercial activities in hospitals and access to treatment under the HE, as intended by the EC [9,14], is undermined when stringent data provisions approach requirements for central authorization (e.g., BE).

It has been argued that the HE undermines commercial ATMP development for central authorization, and even impedes patient access in the future if used inappropriately [10,18,39,42,49]. On the contrary, it is questionable whether

it is commercially viable to develop all ATMPs via the central authorization pathway [50]. Not all ATMPs that are administered to humans may be intended for commercial development. The HE could enable manufacturing of particular therapies for which incentives for commercial development are lacking. Our results underline that the distinction between HE manufacturing for noncommercial purposes and commercial innovation has become blurry after national implementation [9], and the tension between noncommercial and commercial activities varies among countries. This tension is most evident in DE where the HE approaches the procedure for national authorization and restrictive provisions are lacking. Together with a relatively large ATMP developer field, the HE facilitates national market entry of ATMPs regardless of centralized ATMP marketing authorizations. Developers that are located in other EU countries cannot use the HE in the same manner. Thus, HE licenses provide a competitive advantage to developers located in DE, compared with developers in other EU countries. ATMP market withdrawals have occurred in the past, and are illustrative of pricing and reimbursement issues in the EU [50,51]. Competition between HE products and marketed ATMPs for reimbursement may lead to future market failures of centrally authorized ATMPs. Thus, even though HE licenses may benefit patients in DE for a short term, it is undesirable to manufacture ATMPs for the national German market under the HE. These practices also seem to conflict with the intended purpose of the EC to regulate ATMP manufacturing within clinical practice that is not intended for the market.

The heterogeneity of ATMPs and the specificity of their modes of action have important implications for how they are best regulated in relation to the commercial value of an individual GCT. GCTs have a 'precision medicines' approach to treat individual patients or subgroups of patients [52]. However, not all ATMPs that target rare diseases are suited for orphan drug designation [15], or they have low commercial value due to limited intellectual property options for example or high risk profiles for development [15,53]. Thus, some may be better regulated within clinical practice settings under the HE. Other GCTs with commercial value are better suited to be transferred to competitive environments in order to facilitate market entry [53,54]. Some central coordinating bodies already provide support to determine the commercial value of GCTs and opportunities for reimbursement, which is best determined in early phases of clinical development [55]. More consideration of commercial aspects in early development, on top of considerations of 'small-scale' manufacturing could facilitate an optimized use of exemption pathways versus pathways for commercial development, in a complementary fashion. However, criteria to determine commercial values are likely to be a moving target because of scientific and technological advance. Although it is reported that certain cell types, including lymphocytes, chondrocytes, dendritic cells and stem cells, have been manufactured under HE licenses [22], transparency on more detailed product characteristics and motivation to manufacture under the HE are lacking. Public registries could increase clarity on HE manufacturing across the EU, and facilitate collaboration and coordination among public facilities and informed decision making for commercial development [39].

Conclusion

In conclusion, this paper showed how the implementation process of the HE and its outcomes in terms of regulatory licensing provisions and the amount of licenses differed substantially among EU countries. The observed differences among countries are closely related to priorities in the implementation process to issues of unmet medical need, benefit and risks, and innovation. It is complex and uncertain to assess what the implications of these prioritizations are for availability, public health and innovation across countries. It is imperative that competent authorities carefully consider and provide clarity for which kind of activities the HE should be used, and monitor how provisions facilitate appropriate use in clinical practice while safeguarding public health and maintaining incentives for commercial GCT development.

Summary points

- The Hospital Exemption (HE) was enacted to accommodate manufacturing of advanced therapy medicinal products (ATMPs) for treatment purposes. However, how its implementation compares among countries of the EU is largely unknown.
- The aim of this study is to compare how the HE has been implemented in nine EU countries focusing on two outcomes: national licensing provisions and the amount of HE license holders. We also document characteristics of the national implementation process, and how characteristics are associated with outcomes.
- National licensing provisions vary for the HE due to discretionary interpretation of Article 28. Authorities considered unmet medical need, benefits and risks, and innovation in various ways for their intended purpose for the HE.
- In some countries, national licensing provisions resemble the basic provisions that were laid down in EU legislation. In other countries, authorities implemented additional provisions that mandate evidence of positive clinical outcomes for HE authorization or provisions that restrict access to therapies under the HE for which licensed alternative treatment is lacking, among others.
- Judged by the amount of public license holders per country, manufacturing of noncommercial ATMPs for treatment purposes is facilitated under the HE in three countries (Finland, France and the Netherlands). For Italy, license holders remain to be investigated.
- Limited national capacity to comply with provisions, implementation delays, and the use of alternative pathways limits utilization of the HE in four countries (Austria, Belgium, Spain and United Kingdom).
- The HE can be used as a stepping-stone toward commercial development in Germany and Spain. Judged by the amount of private license holders and lack of restrictive provisions, the HE has provided a competitive advantage for German developers compared with commercial developers in other EU countries.

Author contributions

Conceptualization of this manuscript was done by DGM Coppens, H Gardarsdottir, P Meij and J Hoekman. Methodology was designed by DGM Coppens, H Gardarsdottir and J Hoekman. Investigation of this study was done by DGM Coppens. The original draft was written by DGM Coppens and J Hoekman. The written draft was reviewed and edited by H Gardarsdottir, ML De Bruin, P Meij, HGM Leufkens and J Hoekman. The supervision of this manuscript was performed by H Gardarsdottir, ML De Bruin, HGM Leufkens and J Hoekman.

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