Study on the Hospital Exemption

Final Report

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Study on the Hospital Exemption

Final Report

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Directorate-General for Health and Food Safety
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Executive Summary

Background

The ‘Hospital exemption’ (‘the HE’) is specific to ATMPs. It has been established by the ATMP Regulation (Article 28), which amends the European Union (EU) general pharmaceutical legislation (Article 3.7 Directive 2001/83/EC)

Directive 2001/83/EC, in its Article 3.7 specifies that the Directive 2001/83/EC does not apply to ATMPs that are:

- prepared on a non-routine basis and according to specific good practice requirements.
- used within the same Member State, in a hospital, under the exclusive professional responsibility of a medical practitioner.
- provided to meet an individual medical prescription for a custom-made product for a determined individual patient.

The HE framework allows, under specific conditions, the manufacturing and use of ATMPs in Member States, without requiring obtaining a marketing authorisation as per EU pharmaceutical legislation. However, it necessitates authorisation by NCAs and compliance with certain national requirements related to traceability, quality and pharmacovigilance. Differences in how the legal framework for HE was set have led to a diverse picture across Member States. To obtain an overview of the current HE situation in each country, DG SANTE and HaDEA commissioned a Study on Hospital Exemption to a consortium led by PredictBy Research and Consulting, in collaboration with Empirica, Intellera Consulting and Cecoforma. The study took place between September 18, 2023, and April 4, 2025 (18.5 months). The main objective of the study was to address knowledge gaps regarding the implementation of the Hospital Exemption (HE) in national legislation and its outcomes in Member States.

Methods

The study employed a mixed-method approach, combining data collection through a literature review and website search with stakeholder engagement via interviews, a stakeholders’ event, and a targeted survey. The main stakeholder groups included (1) National Competent Authorities (NCAs), (2) HE-ATMPs manufacturers and (3) relevant (inter) national umbrella organisations.

By integrating findings from these various sources, the study team was able to prepare this final report along with 19 in-depth Member State reports.

Results

The available information and methodology used for the study confirmed that 19 out of 27 Member States have adopted national rules that provide a framework for the HE (AT, BE, DE, DK, EE, ES, FI, FR, IE, IT, LT, NL, PL, PT, SE, SI, CY, CZ, MT). Three of these Member States have established a national legal framework for the HE but have not yet had any products available (CY, CZ, MT). Estonia and Sweden are currently working on updating their HE legislation.

In terms of national frameworks for the HE, Belgium, Germany, Estonia, and the Netherlands provide the clearest definitions of "non-routine". Some national provisions specify restrictions on when the HE cannot be used. These restrictions may apply in situations such as when starting a clinical trial is considered possible; when there is an ongoing clinical trial for the same indication and patient group in which the patient could be enrolled; when a centrally authorised ATMP is available for the same therapeutic indication and patient group; or when an existing HE-ATMP is available for the same therapeutic indication and patient group.

Our study maps 110 HE-ATMPs approved between 2008 and 2025 targeting at least 28 therapeutic indications, with 62 products currently available. The majority are Somatic Cell Therapy Medicinal Products (N=37), followed by Tissue Engineered Products (N=21) and Gene Therapy Medicinal Products (N=4). The duration of HE approval varies significantly across countries, with some offering indefinite validity, and others imposing fixed time limits that require renewals once the period is over. The development of these HE-ATMPs is primarily funded through hospital budgets, with occasional external funding. For the pricing of HE-ATMPs, a cost-based pricing approach is most commonly used.

Out of the 51 HE approval holders identified, 26 are public/academic hospitals, 10 are non-profit institutions / research centres, 14 are private companies, and 1 a private hospital. In most cases, treatment with HE-ATMPs takes place in hospitals separate from the manufacturing site but within the same EU country. Consequently, the private companies are typically involved only in the manufacturing of HE-ATMPs.

The duration for reviewing an application by NCAs varies significantly, ranging from 14 days in Denmark to 210 days in Spain and includes the review of pre-clinical, clinical and safety data. To assist applicants in navigating this process, some countries provide additional supporting documents to guide the HE application. Additionally, some NCAs offer the possibility to seek scientific or regulatory advice. Austria, Czech Republic, Finland, Sweden and Slovenia charge a fee for these services, with Portugal, varying the fee depending on the type of approval holder. While most countries have a single authorisation process, others, such as France or Italy, require separate authorisations for manufacturing/establishment and for use/product. Notably Austria does not have

an approval procedure per-se, despite using HE and Denmark incorporates the HE within its compassionate use program.

Belgium, Spain and Germany have the most extensively detailed data requirements to date. In contrast, certain data, such as pre-clinical and clinical data are not required in Poland. The remaining Member States fall between these two ends, with varying degrees of formalisation of data requirements. Pharmacovigilance, traceability, and reporting requirements further enhance oversight and accountability.

Conclusions

The Hospital exemption (HE) facilitates access to innovative treatments and occasionally serves as a bridge towards central marketing authorisation, as currently pursued by three HE-ATMP manufacturers. Transparent reporting mechanisms from HE approval holders to NCAs enhance the accountability of the HE governance in MS. University hospitals and academic medical centres play a crucial role in developing HE-ATMPs, providing new treatments opportunities for patients suffering from rare diseases or lacking access to commercial ATMPs. Additionally, networks of European academic institutions can promote knowledge sharing and innovation, further strengthening the EU ATMP ecosystem.

Study participants pointed out the following good practices:

- **Make information on HE-ATMPs (BE, ES, EE, FI, DE) or the list of eligible HE approval holders (FR, PL, SI) publicly available** to enhance transparency and accessibility.
- **Establish well-structured support mechanisms (IT) that** facilitate the application process, offering clear guidance and multiple support channels.
- **Set clear timelines for application revision (BE),** ensuring predictability and efficiency in the approval process.
- **Provide well-defined and precise application data requirements (BE, DE, ES, FR, IT, NL)** to increase clarity for applicants and ensure consistent regulatory standards.
- **Establish regular and clear reporting mechanisms (BE, EE, ES, FI, IE)** to strengthen oversight and compliance through structured reporting.
- **Provide a cost template for clear and transparent price calculations (ES),** aiding those involved in the price-setting approach.

Keywords

Regulation (EC) No. 1394/2007; Advance Therapy Medicinal Products; ATMPs; Article 28 Hospital Exemption; ATMP manufacturers; academic product; marketing authorisation; non-routine.

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Abbreviation	Explanation
ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CT	Clinical trial
DG SANTE	Directorate-General for Health and Food Safety
EBMT	European Society of Blood and Marrow Transplantation
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EU CHMP	European Medicines Agency's Committee for Medicinal Products for Human Use
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GTMP	Gene Therapy Medicinal Product
HaDEA	European Health and Digital Executive Agency
HE	Hospital Exemption
HE-ATMP	Hospital Exemption Advanced Therapy Medicinal Product
MA	Marketing Authorisation
MS	Member State
NCA	National Competent Authority
NGO	Non-governmental organisation
NSA	National Scientific Advice
PIL	Patient Information Leaflet
PRIME	EU Priority Medicines Scheme
PSUR	Periodic Safety Update Report
QP	Qualified Person
RWD	Real-world data
sCTMP	Somatic Cell Therapy Medicinal Product
SmPC	Summary of Product Characteristics
SoHO	Substances of Human Origin
TEP	Tissue Engineered Product

Country codes

Country	Country code
Austria	AT
Belgium	BE
Bulgaria	BG
Croatia	HR
Cyprus	CY
Czechia	CZ
Denmark	DK
Estonia	EE
Finland	FI
France	FR
Germany	DE
Greece	EL
Hungary	HU
Ireland	IE
Italy	IT
Latvia	LV
Lithuania	LT
Luxembourg	LU
Malta	MT
Netherlands	NL
Poland	PL
Portugal	PT
Romania	RO
Slovakia	SK
Slovenia	SI
Spain	ES
Sweden	SE

1. Introduction

The Advanced Therapy Medicinal Products (ATMP) **Regulation (EC) No. 1394/2007** requires ATMPs to obtain marketing authorisation though the centralised procedure outlined in **Regulation (EC) No. 726/2004**, with the evaluation mainly conducted by the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA). One provision under the ATMP Regulation, known as the **Hospital Exemption clause (HE)**, amends **Directive 2001/83/EC** by allowing ATMPs to be exempt from the requirement for marketing authorisation if certain conditions are fulfilled. The authorisation for manufacturing and use of these HE-ATMPs is subject of rules established by the Member States, resulting in varied implementation across Member States.

In September 2023, the European Commission's Directorate-General for Health and Food Safety (DG SANTE) and the European Health and Digital Executive Agency (HaDEA) commissioned a **Study on Hospital Exemption.** This study is, led by **PredictBy Research and Consulting**, in collaboration with **Empirica**, **Intellera Consulting** and **Cecoforma**, under specific contract N 2023 P3 08 and implementing framework contract No HADEA/2022/OP/0012.

The study took place over a period of **18.5 month**, from September 18, 2023, to April 4, 2025. Its aim was to address the **knowledge gaps** regarding the implementation and the functioning of HE in EU Member States. The information presented in this study reflects the situation from the entry into force of the ATMP Regulation on December 30, 2007) until January 2025.

1.1. Background

Under certain conditions, ATMPs may be exempted from the application of EU pharmaceutical framework and subject of NCA authorisation. National Competent Authorities (NCAs) are responsible for authorising the Hospital Exemptions, under specific conditions. These conditions are outlined in Article 28 of the ATMP Regulation amending Directive 2001/83/EC and are summarised in Box 1 below.

Box 1 – Article 28: Amendments Article 3 of Directive 2001/83/EC, stipulating the list of exemptions:

Article 3

This Directive does not apply to:

(…)

(7)

- Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription for a custom-made product for an individual patient.
- Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Source: Regulation (EC) No 1394/2007

Previous studies, including those by Coppens (2020) or Hills et al. (2020), have provided valuable comparative analyses on how competent authorities in different EU Member States apply the HE clause at the national level. These studies highlight **significant variations in the implementation process and outcomes**, particularly regarding national HE rules and the number of HE approvals granted across EU Member States.

HE approval may serve as a first step forward in granting patient access to ATMPs in the case of unmet medical needs and for indications with small patient populations – areas where companies may have limited interest.

In this context, HE is regarded as an **approach to overcome bottlenecks in the development and patient access to ATMPs**. However, it is essential to acknowledge the differences in national interpretations in HE conditions and variations in the way the HE is applied across EU countries.

A dedicated study to **collect additional evidence** on the implementation and functioning of the HE across selected EU Member States was needed to **provide further insight into the role of HE across the entire ATMP pathway –** spanning from basic research and pre-clinical studies to clinical trials, product development, and ultimately, the delivery of these therapies within healthcare systems.

Understanding how the HE-ATMPs have been regulated across Member States, allows to identify the **lessons learned and good practices**. in view of ensuring that treatment standards are consistently met**, HE provides safe and high-quality options while boosting access to innovative therapies** and facilitating the continued development of these groundbreaking treatments.

1.2. Objectives and scope

The general objective of this study is to **give an overview regarding the national rules providing frameworks for HE and the functioning of HE in EU Member States**. This HE study covers the implementation of HE in the EU from the entry into force of the ATMP Regulation (30 December 2007) until January 2025, with an additional **in-depth focus on the 19 EU Member States**. Moreover, it gathers information on other international regulatory frameworks for innovative products.

Given that **NCAs will, in the future**[(1)], **be required to report data on the use, safety, and efficacy of HE-ATMPs to the EMA** - and that the EMA will establish a repository for this data, including information on the authorisation, suspension, or withdrawal of HE approvals - this study also aims to **propose set of data to be considered for the national implementation report**.

1.2.1. Specific objectives

Based on the general study objective, specific objectives were defined in the areas of mapping, interplay with other legal frameworks, and recommendations for supporting implementation[(2)]:

Mapping

1. **To map and to evaluate the role of research in the field of ATMPs** in university hospitals and other academic & research institutions and its translation to clinical practice. In particular, the study maps the use of HE within these institutions in the EU to bridge the continuation of treatment of patients between different phases of ATMPs clinical development or to treat patients outside clinical trials and the extent to which HE allows patient access to ATMPs that have been successful in clinical practice but are not available on the market.
2. **To map and engage national authorities and relevant stakeholders** in the EU, including the different actors involved in the preparation and supply of ATMPs; university hospitals, academic medical centres, other academic & research institutions, ATMPs manufacturers which hold HE approvals (both public and private entities), substances of human origin (SoHO) establishments, non-governmental organisations (NGOs).
3. **To map how the amendment introduced, by Article 28 of the ATMP Regulation** to Directive 2001/83/EC **has been addressed through**

(1) According to Article 2(7) of the Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC.

(2) Not all objectives were addressed to the same extent in the study.

national law by each EU Member State, the different actors involved and the different practical implementations and aspects of implementation in national laws.

4. **To identify how the national HE rules served the purpose of HE in the EU legislation**, when considering the actual use of the HE and measure the outcomes of HE implementation in terms of national HE criteria, rules and number of HE approvals in each EU Member State.

5. **To provide an overview of the total number of HE products per selected EU country and per category** together with concrete examples of HE products with reference to the HE authorisation holder and the manufacturer.

6. **To assess the accessibility and affordability of HE products in the EU:** determine for which therapeutic indications the HE is used, the cost of the therapy, the number of patients treated with HE products and the duration of HE approvals. Compare the uses of the HE in different Member States and assess the impact on patient access to relevant treatments, as well as patient safety.

7. **To provide a general comparison of the EU HE pathway with relevant pathways in other selected jurisdictions** (US, Canada, South Korea, Japan, UK, Switzerland), including for patient access and affordability.

8. **To identify the limitations in the implementation of HE** (e.g., existing national legislation, absence of HE national rules, capacity of ATMP authorisation holders to comply with national HE rules) in the EU.

Interplay with other legal frameworks

9. **To determine whether HE continues to be used when there is an ongoing clinical trial** with an investigational medicinal product for the same therapeutic indication or there is already on the market a centrally authorised ATMP for the same therapeutic indication.

10. **To evaluate how the HE pathway relates to other regulatory frameworks** (clinical trials) and other exemption pathways for manufacturing of ATMPs (compassionate use, named patient use).

11. **To evaluate the relationship between the HE pathway and the ATMP market authorisation** for competition, patient access (EU-wide) and affordability, as well as the respective relevance for innovation activities and investments, including their role in the innovation cycle.

Views from the study participants on practices supporting implementation

12. **To collect sets of good practices, basing on views of study participants,** regarding the collection of data on use and volumes, quality, safety and efficacy of ATMPs manufactured and used under the HE and their reporting to National Competent Authorities (NCAs).

13. **To identify the data set for the national implementation report** that will facilitate the smooth adaptation of NCAs to new reporting requirements of the pharmaceutical legislation.

2. Methodology

The study adopted a **mixed-method approach**, combining data collection through a **literature review** and **website search**, and **stakeholder engagement** via **interviews**, **email follow-ups**, a **stakeholders' event**, and a **targeted survey** to gather primary data for analysis.

The **interviews** served as the primary data source, with the other methods providing supplementary insights. In the study's **inception phase**, a **literature review** was conducted to identify existing data and information on the topic. The knowledge gained, along with insights from an initial set of **exploratory interviews with representatives of EU academic institutions**, informed the creation of an analytical framework, which helped clarify three key areas of study: **legislation**, **application & implementation**, and **outcomes.** These initial steps shaped the development of the **interview guides** used for data collection at Member State level. The subsequent **stakeholders' event** and **survey** further supplemented the data, allowing the study team to confirm, expand, or clarify previously collected information. In some cases, detailed information was not available from every stakeholder contacted, leading to small data gaps highlighted throughout the report.

Combining the findings from different sources allowed the study team to prepare the in-depth Member State reports available in **Annex 1**, which present a detailed overview of HE at country-level.

This chapter provides an overview of the **methodological approaches** applied throughout the study.

2.1. Data collection and consultation activities

2.1.1. Literature review

The focus of the review was to analyse the literature reporting **on the role of academia in the field of ATMPs** and **examining ATMPs manufactured under HE in different countries**. An extensive search was conducted between September 2023 and December 2023 in **Scopus and PubMed** to identify relevant publications. A total of 79 documents were found in Scopus and 59 in PubMed exploring the use of HE in Europe. Results were merged and duplicates removed, and a total of 81 results were screened for relevance by title and

abstract before writing the final literature review narrative. This was the foundation for preparing the analytical framework and the interview guides used to collect data for the Member State reports.

A second, more targeted literature review was conducted between December 2024 and February 2025, to **explore relevant pathways similar to HE to enable patients to receive ATMPs in other selected jurisdictions** (US, Canada, South Korea, Japan, UK[3], Switzerland). We used online web search to identify relevant literature and reviewed the reference lists of articles and reports to find additional relevant sources. These country reports are available in **Annex 2**.

2.1.2. Website search

To complement the **literature review**, the study team conducted an **in-depth search** of the websites of NCAs for official documentation on **HE rules**, including relevant **guidance documents**. In some cases, reports and articles identified during the literature review, which mapped the situation across different EU countries, were used to pinpoint sources of official Member State documentation.

The data gathered from these **website searches** provided the foundation for drafting the initial version of the **Member States report**, which was later expanded and validated through **interviews**. Since many documents were available only in the original national language, the team relied on two online translators: **Google Translate** and **DeepL**. This exercise helped clarify three key areas of study: **Legislation**, **Application & Implementation**, and **Outcomes**.

The initial website search was conducted between September 2023 and January 2024. An updated search was performed in **January 2025** to verify if any changes had occurred, particularly to check if countries that had not previously adopted national frameworks for HE in national law, had made any recent updates.

2.1.3. Targeted interviews

Between September 2023 and January 2024, in parallel with the literature review and website search, the study team reached out to EU-level experts for **exploratory interviews**. From February to July 2024, the study team conducted **in-depth interviews** to gather product and country-specific data. The process began with online interviews with representatives from NCAs, followed by HE-ATMP manufacturers and reimbursement authorities. Other country-level institutions, networks, and individual experts were approached to supplement the data.

[3] Please note that the Hospital Exemption was introduced in the UK in 2010; however, its uptake has been limited due to the availability of alternative pathways. Additionally, given Brexit, the UK is considered in the section on jurisdictions abroad (**Annex 2**).

In some cases, when experts had limited availability or faced language constraints, **written contributions** to the interview questions were accepted as an alternative to interviews. **Follow-up emails** were exchanged to ensure a thorough data collection process, validate findings, and resolve any inconsistencies or gaps. Table 1 below, presents the number of interviews completed and the number of written contributions received per stakeholder type.

Table 1 – Overview of interviews and written contributions per stakeholder type

Stakeholder type	# interviews	# written contributions	**Total**
Exploratory interviews[1]	12	0	**12**
National Competent Authority	16	3	**19**
(HE-)ATMP manufacturers	28	6	**34**
Reimbursement authorities	5	1	**6**
Members of (inter)national organisations[2]	3	1	**4**

[1] Including: European Society for Blood and Marrow Transplantation (EBMT), European Society for Organ Transplantation (ESOT), EURORDIS, Blood Transfusion Association (BTA); Terumo Blood and Cell Technologies (BTC), European Eye Bank Association (EEBA), European Association of Hospital Pharmacists (EAHP), and MedTech Europe.

[2] Including: ATMP platform for translational medicine (EATRIS), Network Officine Terapie Avanzate APS (NOTA APS), Alliance for Regenerative Medicine (ARM), The Belgian Health Care Knowledge Centre (KCE).

Source: Authors' elaboration

2.1.4. Stakeholders' event

On 21 November 2024, a full-day hybrid event took place in Brussels and online, which focused on **"Implementation of the Hospital Exemption in the EU and its Role in Boosting Innovation and Patient Access to Innovative Therapies".**

The event gathered officials from the NCAs and developers of ATMPs, both academic and private, which are actively involved in the implementation of HE in EU countries. Other stakeholders, including from the EMA, the European Society of Blood and Marrow Transplantation (EBMT), pharmaceutical industry associations, scientific societies and academic biotech spin-offs, also delivered presentations or were engaged in useful conversations. Participants were involved in different formats during the event: **in-person** (N=43); **online active** (N=48); **online passive** (N=151).

2.1.5. Targeted survey

Following the Study's event, a survey was launched on EUSurvey to collect feedback on good practices regarding the current implementation of HE in the EU, investigate whether there are other existing good practices to support

national regulators and ATMP developers, and understand the impact of these practices on enabling patient access to ATMPs and boosting innovation around ATMPs.

The survey was disseminated among stakeholders who had been involved in the study or attended the event (N=340). While primarily targeted at these groups, respondents were allowed to share it within their networks of ATMP stakeholders. The survey remained open for one month, with two reminders sent following the initial invitation.

A total of 119 stakeholders responded to the survey. Table 2 below presents an overview of survey respondents by type of organisation. The survey questions as well as the statistics on survey responses by country are available in **Annex 3**, and results are presented in **Annex 4**. To ensure a meaningful interpretation, the study team has carefully analysed the results, contextualising and identifying recurring patterns in responses.

Table 2 – Survey respondents by type of organisation

Organisation	Respondents
Academia	30 (25%)
National Competent Authority (NCA)	20 (17%)
Healthcare provider (e.g., hospital, pharmacy)	10 (8%)
Non-profit research organisation	10 (8%)
Healthcare professional	8 (7%)
Large pharma company	8 (7%)
Biotech SME (micro-small, or medium-sized enterprise)	6 (5%)
Patient organisation or advocacy group	5 (4%)
Regulatory/public authority (other than NCAs)	4 (3%)
Contract manufacturing organisation	2 (2%)
Contract research organisation	1 (1%)
Scientific society	1 (1%)
Other[1]	14 (12%)
Total	**119 (100%)**

[1] Other including: Trade/industry associations (x6), Non-profit organisations (x4), Independent professionals (x2), Biotech and biopharmaceutical companies (x2).

Source: Authors' elaboration based on survey results

2.2. Good practices of implementation identified by study participants

The identification of good practices in the implementation of HE across Member States was done by study participants. National approaches were reviewed to determine commonalities and deviations in HE implementation, allowing for the

extraction of examples of good practices. These good practices are highlighted in the results section. While the methodology was primarily qualitative and descriptive, the selected examples were those highlighted by the study participants. Given the nature of the data collection, we recognise that this is not an exhaustive assessment but rather an aggregation of relevant insights from the consulted sources.

2.3. Development of a national implementation report template

When identifying relevant data sets for the purpose of national implementation reports, a multi-step methodology was applied:

- **Review of existing national reporting practices:** An analysis was conducted to assess the reporting frameworks currently in place across different EU Member States. This involved identifying whether NCAs already collect structured data on HE-ATMPs and, if so, the format, scope, and level of detail of these reports.

- **Identification of key reporting elements:** Based on the review of existing practices and the anticipated EMA reporting requirements, the study identified the relevant elements that may be necessary for a comprehensive national implementation report. This included both the information required for internal NCA assessments and the key points that should be submitted to the EMA.

    - **Template development:** Drawing from the findings of the first two steps, a possible draft structure for the national implementation report was formulated. The focus was on ensuring clarity, usability, and completeness. The template was designed to capture essential data sets, such as product characteristics, clinical outcomes, safety monitoring, and regulatory decisions, in a structured manner. The template includes data fields for reporting of aggregated data and a proposal for reporting data on patient and product level, where applicable.

This template is presented in **Annex 5.**

3. Results

3.1. Overview of Hospital Exemption in Member States

3.1.1. Regulatory implementation of the Hospital Exemption Clause

The study participants consider HE as an enabler for facilitating timely patient access to safe and efficacious ATMPs, particularly when there is no availability of commercial ATMPs on national market or there are no other treatment options. By allowing tailored solutions for individual patients, the HE provides flexibility in treatment options for patients' needs. Figure 1 below illustrates the level of HE activity across Member States, showing the total number of HE products approved in each country.

Figure 1 shows that based on the information available and methodology of the study it was found out that:

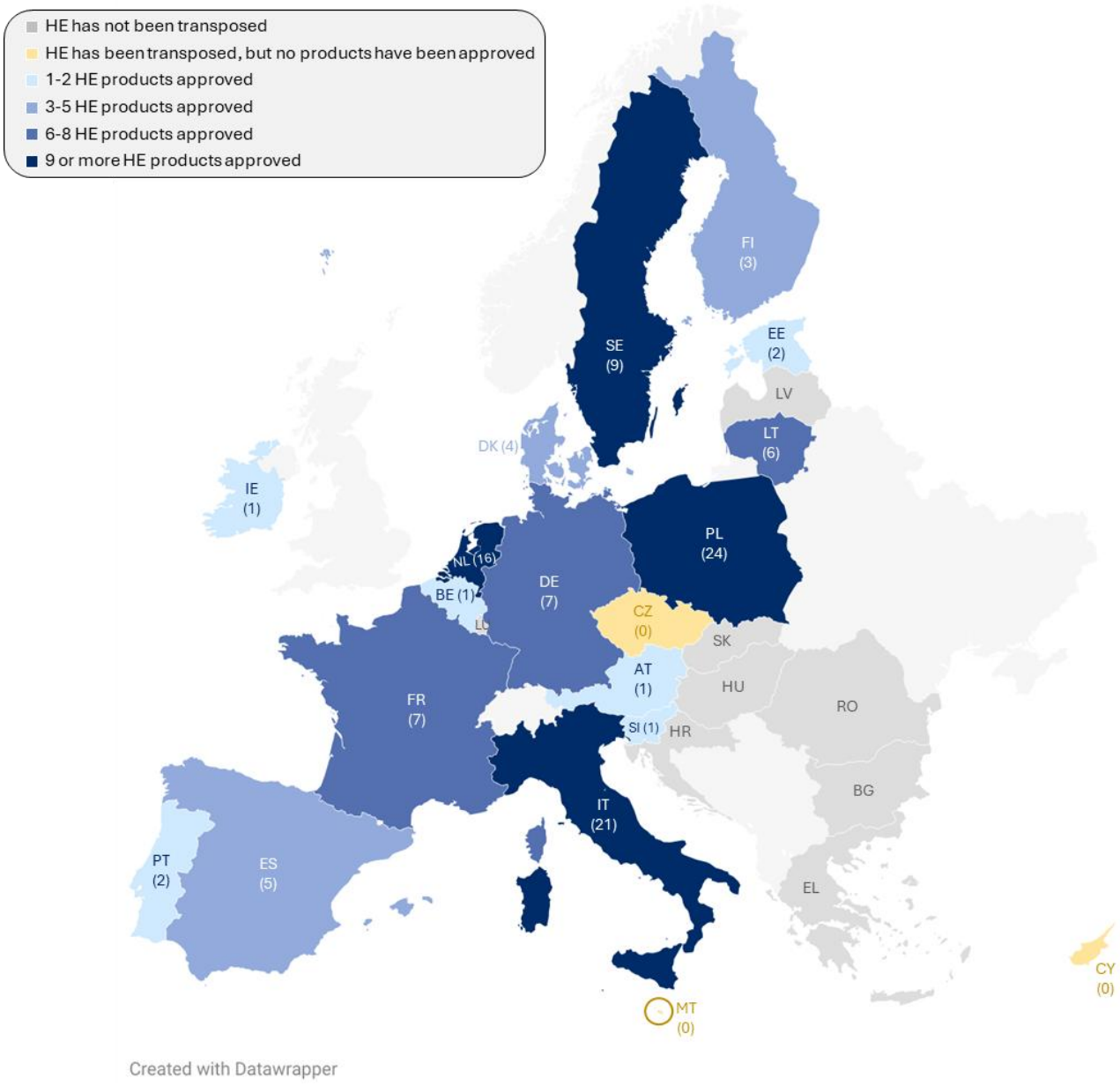
- **19 out of 27 Member States** have established specific requirements in their national laws for the HE framework and **16 out of them** currently have (or previously had) products available under the HE: AT, BE, DE, DK, EE, ES, FI, FR, IE, IT, LT, NL, PL, PT, SE, SI. At present, two of these countries – EE and SE – are working on an updated version of their legislation. Links to the related legislative documents can be found in **Annex 6**.

- **3 out of 27 Member States** have established a framework for HE in national law but have not yet had any products available: CY, CZ, MT.

- **For 8 out of 27 Member States** it was not possible, based on the study's methodology to determine how the HE is applied in BG, EL, HU, HR, LU, LV, RO, SK.

While this study highlights the how the HE has been addressed in the national law of the Member States based on the available information and methodology used in the study, it does not explore the underlying reasons for potential non-existence of national rules on HE in certain countries or where information was not available. An in-depth review of official websites and publicly available resources in January 2025 indicated that these countries have not yet adopted specific national provisions. There is no public information suggesting if or when these Member States might consider introducing national rules on the HE in the future.

Figure 1 – Overview of level of activity per Member State



Country abbreviations: AT = Austria, BE = Belgium, BG = Bulgaria, CY = Cyprus, CZ = Czechia, DE = Germany, DK = Denmark, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, FR = France, HR = Croatia, HU = Hungary, IE = Ireland, IT = Italy, LT = Lithuania, LU = Luxembourg, LV = Latvia, MT = Malta, NL = the Netherlands, PL = Poland, PT = Portugal, RO = Romania, SE = Sweden, SI = Slovenia, SK = Slovakia.

Source: Authors' elaboration based on collected data

3.1.2. National provisions regulating the Hospital Exemption

Definition of non-routine

HE may be relied upon if a product is s prepared on a "non-routine basis" are excluded from its scope; however, the term is not clearly defined, leaving individual countries to interpret it independently.

Table 3 – Interpretation of "non-routine"

Interpretation of non-routine	Country
Not specified	AT, CY, LT, MT
Products prepared on an **individual basis**[1]	CZ, DK, FI, FR, IE, IT, PT, SI
Products prepared in **small quantities**[2]	BE, DE, EE, ES, FR, NL, PL, SE

[1] This does not mean that only one patient can be treated with a given approval.

[2] Incl. occasionally prepared, non-industrial, prepared on an ad-hoc basis, non-systemic manner.

Source: Authors' elaboration based on collected data

Belgium, Germany, Estonia, and **the Netherlands** provide the clearest definitions of "non-routine", as outlined in Table 4 below. Only two countries have established explicit numerical limits: Estonia and the Netherlands, both setting the limit at 10 patients, with certain exceptions allowed in the case of the Netherlands and a revision of this definition envisaged in Estonia.

Table 4 – Examples of definition of non-routine

Country	Definition of non-routine
BE	No fixed number of patients has been defined for treatment under HE. According to the Royal Decree, the preparation of an ATMP is considered non-routine if: • It is prepared on a **small scale** with a low frequency of batch preparations, or • It is administered to a **small number** of patients. As a reference for what qualifies as non-routine, the number of patients treated in a phase I clinical trial - typically 20 to 30 patients - is considered.
DE	A medicinal product is not routinely manufactured if one of the following conditions applies: • The medicinal product is manufactured on a **small scale** and there are variations in the manufacturing process that are medically justified for an individual patient. • The medicinal product has not yet been manufactured in sufficient quantities, so the necessary knowledge for a comprehensive product evaluation is not yet available.
EE	The scope of HE has been outlined by establishing specific thresholds for critical elements of the EU's ATMP regulation, including the concept of non-routine use which considers two main factors: a time limit of **two years** and a maximum of **10 patients**.
NL	Non-routine use is understood as ATMPs prepared on a **small scale**, which is further specified as a maximum of **10 patients** that can be treated throughout the approval period of one year (with exceptions). As a general guideline, applicants may consider as non-routine: • ATMP prepared from autologous cells; • ATMP prepared from non-autologous cells but specific to one patient; • ATMP prepared on a small scale.

Source: Authors' elaboration based on collected data

HE approval duration

HE approval durations vary widely across countries, with some offering indefinite validity, while others impose fixed time limits requiring renewals once the period is over.

Table 5 – HE approval duration

Duration	Country
One-time authorisation: single patient treatment for a specific patient	IT
1 year	NL, PT
2 years	CZ, DK, EE[1], LT
3 years (extension 5 years)	ES
Case by case, usually 3-5 years	DE
5 years	FR[2], SE
Indefinitely (inspections every 1-3 years)	AT[3], BE, FI, IE, PL, SI

[1] Amendment proposal suggests that approval period will remain two years and can be extended for a period of five years.

[2] In **France**, this applies to the first renewal of the 'HE establishment authorisations', which is not needed for future rounds and the HE product approval has no time limit.

[3] In **Austria**, this applies to 'GMP compliance'.

Source: Authors' elaboration based on collected data

Eligible HE approval holders

Eligibility criteria for HE approval holders vary across countries. While the majority of HE approval holders are public and non-profit entities involved in healthcare and medical research, private companies are also active. From the 51 approval holders mapped, 26 are public/academic hospitals, 10 are non-profit institutions/research centres, 14 are private companies, and 1 a private hospital.

Table 6 – Eligible HE approval holders

Restriction	Country
Public and private organisations (including hospitals)	BE, DE, EE[1], FI, IE, LT, NL[2], PL, SI, AT[3]
Healthcare or hospital institutions (public and private)	CY[4], DK, PT, SE[4], ES, FR, CZ, IT

[1] HE-ATMP can be manufactured by a company, but the application must be submitted jointly with the treating hospital.

[2] Restricted to hospitals and companies

[3] No HE approval holders per se, application via GMP; [4] Not defined if both public and private or just public. Information not specified in **Malta**.

Source: Authors' elaboration based on collected data

See Annex 4 for: Survey responses on eligible HE approval holders

Manufacturing and treatment locations

In most cases, treatment with HE-ATMPs can take place in hospitals separately from the manufacturing site. This has been seen in countries such as **Austria, Belgium, Czechia, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Lithuania, Poland,** and **Slovenia**, where products can be administered at various hospitals. In **Denmark**, an additional application is needed for each treatment location.

Some countries link treatment locations directly to the **HE approval holder's manufacturing site**. This is the case in **Spain, the Netherlands,** and **Portugal**, where treatments are typically administered at the same location as the approval holder's manufacturing site. **Sweden** adds a regional component, allowing treatments at the HE approval holder's site and at other locations within the same healthcare region. This information is not specified for **Cyprus** and **Malta**.

Intended purpose and motivation to use the HE

For most countries, the primary rationale of the HE is to address **unmet medical needs**, ensuring patient access to treatments that would otherwise be unavailable (i.e., in most countries, this is defined as a situation where no therapies with central marketing authorisation exist for a given indication, or when pricing and reimbursement agreements have not been reached in a country and therefore the centrally authorised ATMPs are not available at the national market).

Table 7 – Motivation to use the HE

Use of HE	Country
Address unmet medical needs	All except for CY, LT, and MT, as these countries have not (explicitly) defined an intended purpose.
No commercial alternatives available / last resort treatment	BE, CZ, DK, EE, FI, FR, IE, IT, NL, PL, PT, SE, SI
To treat patients when clinical trials are not feasible	BE, CZ, FI, FR, LT, PL
Treatment for patients who are not eligible for ongoing clinical trials	NL
Bridge between clinical trials	NL
Bridge towards central marketing authorisation	DE, EE, ES, NL
For products that are not suitable for industrial manufacturing and/or have no commercial viability	CZ, ES, SE, IE
Allowing tissue-based and cell-based products to remain on the national market	AT
Life-threatening situations	FR, IT

Source: Authors' elaboration based on collected data

See Annex 4 for: Survey responses on pursuing Central Marketing Authorisation

Restrictions for using the Hospital Exemption

National provisions in some countries outline specific restrictions for the use of HE, as detailed in Table 8 below.

Table 8 – Restrictions for using the Hospital Exemption

Country	CT instead	CT ongoing	ATMP available	HE available
BE		✓	✓ [1]	✓
CZ			✓	
DK			✓ (exceptions)	
EE			✓	✓
FI	✓	✓	✓	
FR	✓	✓	✓	
IE			✓	
IT			✓	
NL	✓	✓	✓	✓
PL		✓ (unofficial)	✓ (unofficial)	✓ (unofficial)
PT			✓ (in practice)	
SE		✓	✓	
SI	✓			

[1] In BE this means also through a *compassionate use program* or *medical need program*.

Restrictions include: when starting a clinical trial is considered possible **(CT instead)**; when there is an ongoing CT for the same indication and patient group in which the patient could be enrolled **(CT ongoing)**; when there is a centrally authorised ATMP for the same therapeutic indication and patient group **(ATMP available)**; or when there is an existing HE for the same therapeutic indication and patient group **(HE available)**.

Source: Authors' elaboration based on collected data

In some cases, such as in **Germany** and **Spain**, restrictions are determined on a case-by-case basis, providing flexibility depending on the circumstances. **Austria, Cyprus, Lithuania,** and **Malta** do not specify such restrictions in their national provisions. Additional specific restrictions may also apply; for further details, refer to the Member State reports in **Annex 1**.

3.1.3. Application process, guidance and data requirements

Guidance documents

Some countries provide further supporting documents to guide the HE applicants. In addition, some NCAs offer the possibility to ATMP developers to seek scientific

or regulatory advice. Table 9 outlines the provided information and guidance by country.

Table 9 – HE application process and guidance

Provision of	Countries
Application form[1]	BE, CZ, DE, DK, EE, ES, FI, FR, IE, IT, LT, NL, PL, PT, SE
Guidance documents	BE, CZ, DE, DK, ES, FI, FR, IE, IT, NL, PT, SE
Scientific and regulatory advice	AT, BE, CZ, DE, DK, EE, ES, FI, FR, IE, IT, LT[2], NL, PT, SE, SI
Fees for advice or application	AT, CZ, FI, PT[3], SE, SI

[1] In some countries, applicants must apply for different types of authorisations, which are not always referred to as HE approvals. For instance, manufacturer's authorisation (**Ireland**), manufacturing authorisation and authorisation for use/product (**Italy, France, Poland**), compassionate use permit (**Denmark**).

[2] Upcoming.

[3] Fees charged only for private institutions, might be the same in EE in the future.

Source: Authors' elaboration based on collected data

Austria does not have a specific authorisation process for HE products, and therefore an application process does not apply. In this case, the only requirement prior to the manufacture of HE-ATMPs is to have a GMP certificate in place. Details regarding the application process and guidance are missing for **Cyprus** and **Malta**, as these countries have provided national framework for the HE but there has been no activity to date.

Maximum duration of application review

The duration of an application review ranges from 14 days in **Denmark** to 210 days in **Spain**. These timelines can vary significantly across countries and even within the same country, depending on the stage of product development, the comprehensiveness of the submitted data, and the review process in place. The timelines exclude clock stops, which occur when the NCA issues comments or requests for additional documents. However, the review process often takes longer than the reported durations.

Table 10 – HE application process and guidance

Provision of	Countries
Less than 50 days	CZ, DK, LT, NL
Between 51 and 100 days	AT[1], FI, IE, IT[2], PL, PT
Between 101 and 150 days	BE, DE, EE, FR, SE
Between 151 and 200 days	SI
More than 200 days	ES

[1] Refers to GMP certificate application. Information not specified in **Cyprus** and **Malta**.

[2] Depending on the urgency of the case, the timeframe can be shorter than 50 days, with some urgent cases being approved in under 10 days.

Source: Authors' elaboration based on collected data

Pre-clinical, clinical and quality data requirements

The specific pre-clinical, clinical, and quality data requirements vary across national legislations. In some cases, assessments of HE applications are conducted on a case-by-case basis, meaning that requirements may not always be predetermined but are instead evaluated in the context of individual applications.

Belgium, Spain and **Germany** are the countries with the strictest data requirements to date. In **Austria** and **Poland** certain types of data are not required or not evaluated. The remaining Member States fall between these two ends, with varying degrees of formalisation of data requirements (except countries like **Cyprus** and **Malta** where the HE has not yet been used).

While Table 11 below provides an overview of the requirements in each country where specific framework for HE was introduced in national law, **Annex 1** offers a comprehensive overview of each country's approach. Despite some heterogeneity among Member States and NCAs, there is a strong emphasis on GMP and quality requirements, with significant alignment in this area.

Table 11 – Minimum data requirements

Data	ES	BE	DE	FR	CZ	DK	EE	NL	IT	FI	SE	PT	IE	LT	SI	PL	AT	CY	MT
Pre-clinical																			
Clinical																			
Quality																			
GMP																			
Total products approved	5	1	7	7	0	4	2	16	21	3	9	2	1	6	1	24	1	0	0

Colour	Description
	No specified data requirements: Countries may have further requirements that are requested during the application process or are not formally defined.
	No mandatory data requirements: Data is required or requested only when available. This primarily applies to pre-clinical data requirements.
	Mandatory, but no formal minimum data requirements: Data is required or requested on a case-by-case basis, depending on the type of product and indication. The goal is to ensure that the benefits of the medicinal product outweigh potential risks.
	Formalised data requirements: Clinical trial data is explicitly encouraged or preferred. However, the final assessment remains case-by-case.
	Higher level of formalisation of requirements: Clinical trials data is explicitly requested (but for example in Spain, if the HE product was used before the entry into force of the ATMP Regulation, RWD from previous treatment of patients with the product is also considered as supporting data).

Source: Authors' elaboration based on collected data

3.1.4. Pharmacovigilance, traceability and reporting

Pharmacovigilance

Countries have a pharmacovigilance system in place to monitor the safety of HE-ATMPs as defined in Article 28 of the ATMP Regulation. These systems typically outline how adverse events should be recorded, stored, and reported, whether special training is required, and the specifics of a risk management plan. In **Czechia** and **Poland**, there is no formalised pharmacovigilance procedure.

Regulations across countries emphasise the importance of a risk management plan, particularly for specific, high-risk HE-ATMPs that could pose significant risks to individual patients or public health. This requirement is explicitly highlighted in **Belgium, Estonia, France, Germany, Ireland, Italy, Lithuania, the Netherlands, Spain,** and **Sweden**. Additionally, these countries require a Qualified Person (QP) or a designated responsible individual to be available 24/7.

Routine inspections are conducted in some countries to ensure compliance with pharmacovigilance requirements, either regularly or on a case-by-case basis. This is explicitly documented for **Belgium, Finland, Ireland, Lithuania, the Netherlands,** and **Sweden**, though similar practices may exist in other countries even if not formally described.

Reporting mechanisms

Most countries require HE approval holders to report activities related to active HE products and some NCAs establish additional reporting requirements for complete oversight.

Table 12 – Reporting mechanisms in EU MS

Reporting	Countries
General safety reporting as required by ATMP Regulation (of adverse events, PSURs) [1]	BE, CZ, DE, DK, EE, ES, FI, FR, IE, IT, LT, NL, PT, SI, SE
Additional MS specific safety reports/annual reports	BE, CZ, EE, FR, NL, PT, ES, SI
Not defined	AT, CY, PL, MT

Source: Authors' elaboration based on collected data

When assessing the reporting mechanisms regarding the availability and use of HE-ATMPs, it is important to distinguish between the purpose of **repository of approvals** versus **clinical data registries**. More on this is provided in **Annex 4**.

See Annex 4 for: Survey responses on the use of HE-ATMP registries

Traceability

Traceability systems aim to ensure that HE-ATMPs remain traceable throughout their journey, from sourcing of critical raw materials to manufacturing and administration to patients. Traceability systems are specifically required in all countries, but are not further formally described for **Austria**, **Cyprus** and **Malta**.

In line with the ATMP Regulation, traceability systems are explicitly specified for **Belgium, Finland, Ireland, Lithuania, the Netherlands, Portugal, Slovenia, Spain,** and **Sweden.**

3.1.5. Pricing and reimbursement

Pricing and reimbursement of HE-ATMPs

According to the Transparency Directive 89/105/EEC, MSs should publish reimbursement lists at least once a year [(4)]. However, there is limited information available regarding the pricing and reimbursement of ATMPs produced under HE. In most countries, these aspects are not the competency of NCA and are managed by other institutions within the country, such as procurement agencies.

The development of HE-ATMPs is primarily funded through hospital budgets, with occasional external funding. In **Spain** and **Italy**, for instance, national, academic, or industrial funds, as well as sponsors, may support the development of HE-ATMPs (i.e., ARI-0001 in Spain was funded by several public grants and a crowdfunding program[(5)]).

Reimbursement of HE-ATMPs varies across MS. In some countries such as **Germany** or **Spain**, reimbursement practices may vary depending on the type of therapy or the nature of the approval holder (e.g., private companies versus non-profit organisations). Out-of-pocket payments are reported in countries like **Lithuania** and **Poland**.

A cost-based pricing approach is most often used for HE-ATMPs, factoring in manufacturing and treatment costs, and sometimes even societal costs. This approach is observed as the baseline in **Finland**, **Ireland**, **Lithuania**, the **Netherlands**, **Portugal**, **Sweden**, **Denmark**, **Estonia**, and **the Netherlands**. In **Spain**, an incentive for research has been established, allowing manufacturers

[(4)] For more information, see EC publication that includes country fiches and links to the national websites where information on reimbursed products is published: Functioning of Directive 89/105/EEC relating to the transparency of measures regulating the prices and reimbursement of medicinal products ('Transparency Directive') - Publications Office of the EU

[(5)] For more information on the ARI Project, visit: https://www.clinicbarcelona.org/en/news/aemps-authorises-hospital-clinics-car-t-ari-0001-for-patients-with-acute-lymphoblastic-leukaemia

to recover some of the investment cost, which is then used to maintain the infrastructure that is needed for sustaining the treatment[6]. In **Poland**, cost-plus pricing is used[7].

Details on how the pricing and reimbursement of HE-ATMPs is set remain unclear in **Austria**, **Belgium**, **Cyprus**, **Czechia**, **Malta**, and **Slovenia**.

3.1.6. Overview of Hospital Exemption products

Publicly available information on HE-ATMPs

In addition to the national provisions regulating the HE, several countries have dedicated websites with information on HE products available. The information may include product name, HE approval holder, date of approval, and in some countries also a summary of product characteristics (SmPC) and the patient information leaflet (PIL).

- **Belgium**: Hospital exemption for ATMPs [In Dutch and French]
- **Spain**: List of authorisations for use [In Spanish]
- **Estonia**: Hospital exemption permits issued by the Estonian Medicines Agency [In Estonian]
- **Finland**: Current cell therapy products manufactured at the ACTC [Published by the manufacturer]
- **Germany**: Advanced Therapy Medicinal Products [By type of ATMP - can be identified for the “PEI” as prefix for the licence number]

Type of therapies

In total, the study team managed to map information for 110 HE-ATMPs available at some point between 2008 and January 2025. Table 13 below compares the currently available HE-ATMPs to the numbers of ATMPs with central marketing authorisation. Numbers were retrieved from NCAs and manufacturers and it is estimated that 62 HE-ATMPs are currently available. For further details, such as

[6] **[In Spanish]** Price proposal for non-industrially manufactured advanced therapy medicinal products. Standardised price calculation sheet. Available at: https://www.sanidad.gob.es/areas/farmacia/infoMedicamentos/terapiasAvanzadas/docs/20191014_Anexo1_Propuesta_precio_MTA_no_industrial_SNS_CISNS.pdf

[7] Cost-plus pricing (CPP): CPP is the principle of setting the price of a product based on its costs of production plus a profit margin (for example, a percentage of the costs of production, or a fixed profit). When estimated for CPP purposes, costs of production typically include manufacturing costs, costs associated with regulatory processes and compliance, and overhead and other operational expenses (World Health Organization, 2020).

approval durations, manufacturing sites, and treatment locations, please refer to **Annex 1**.

Table 13 – Approved HE-ATMP by type of therapy

Type of ATMP	Total approved HE-ATMPs 2008-2025	Currently available HE-ATMPs	Currently authorised ATMPs
Somatic Cell Therapy Medicinal Products (sCTMP)	59 (54%)	37 (60%)	1 (5%)
Tissue Engineered Products (TEP)	25 (23%)	21 (34%)	2 (11%)
Gene Therapy Medicinal Products (GTMP)	12 (11%)	4 (6%)	16 (84%)
Not identified[1]	14 (13%)	0	0
Total	**110**	**62**[2]	**19**

[1] In some cases the NCA provided the total number of approved HE-ATMPs but could not share details on the type of product and/or the manufacturer of the product. In some cases, this information could be further complemented by the manufacturer, but when the manufacturer remained unknown or was unresponsive, this information is missing and is presented in this table as "not identified"; [2] Including 24 products for Poland and 6 for Lithuania, but it's not clear whether these products are currently available.

Source: Authors' elaboration based on collected data; EMA CAT quarterly highlights and approved ATMPs February 2025

Table 14 – Number and types of HE-ATMPs

Country	HE products currently available	Total approved HE products	GTMP	TEP	sCTMP	NI[1]
PL	**24**[2]	**24**	2	14	8	0
IT	**N/A**[3]	**21**	8	1	12	0
DE	**7**	**7**	0	5	1	1
FR	**7**	**7**	0	0	7	0
LT	**6**[4]	**6**	0	0	6	0
ES	**5**	**5**	2	1	2	0
NL	**3**	**16**	0	1	8	7
SE	**3**	**9**	0	0	8	1
FI	**2**	**3**	0	0	2	1
EE	**1**	**2**	0	1	1	0
PT	**1**	**2**	0	1	1	0
AT	**1**	**1**	0	0	1	0
DK	**1**	**4**	0	0	1	3
SI	**1**	**1**	0	0	1	0
BE	**0**	**1**	0	1	0	0
IE	**0**	**1**	0	1	0	0
CZ	**0**	**0**	0	0	0	0
CY	**0**	**0**	0	0	0	0

MT	**0**	**0**	0	0	0	0

[1] **Not Identified (NI):** Products for which insufficient information is available to classify them under one of the above categories; [2] Not clear whether this is the total amount of products currently approved, or overall (ever) approved; [3] N/A as HE product approval is based on single-dose administration, and 21 refers to the number of approved HE-ATMPs that have obtained at least one approval in IT; [4] The manufacturer requested a renewal in 2024, but the study team has not received a status update.

Source: Authors' elaboration based on collected data

Patients treated with HE-ATMPs

The figures in the Member State reports in **Annex 1** show the total number of patients treated by country for a total of 64 products – both previously and currently available – for which the study team was able to collect data from NCAs and manufacturers. **These figures should be interpreted with caution, as they could lead to misinterpretation.** The following considerations should be kept in mind:

- While the specific number of patients treated under the Hospital Exemption (HE) was requested, some reported numbers include treatments administered before the ATMP Regulation (EC) 1394/2007 came into force (i.e., before some of these products were considered ATMPs). Some of these products had already been in use by physicians for a significant period and for this reason number of patients treated might be higher than expected.

- The figures may also include patients treated during clinical trials or those receiving the treatment through compassionate use programs.

- In some countries, regulatory changes have occurred over time, meaning that the treatment of many patients is no longer possible under the current legislation.

Therefore, some of the cited high numbers should be regarded as exceptional cases – this has been reflected in specific notes to showcase when this is the case.

Therapeutic indications

Table 15 below provides a detailed overview of the therapeutic indications of HE-ATMPs, covering both currently available and previously used products for which this data is available. Products have been developed targeting at least 28 broad therapeutic indications – information being only available for 83 out of the 110 products identified. The table highlights the number of products targeting specific medical conditions, with the majority targeting viral infections, graft-versus-host disease, osteoarticular disorders, burns, cancer, articular cartilage damage/defects/lesions and diabetes. There are also rare or less common disorders for which one product has been developed, reflecting the versatility of HE-ATMPs in addressing a wide array of conditions and rare diseases.

Table 15 – Therapeutic indication of HE-ATMPs

Indication	Total approved HE-TMPs 2008-2025
Viral infections (CMV, ADV, EBV, JCV)	13
Graft-versus-host disease (GvHD)	10
Osteoarticular disorders (osteoarthritis, osteonecrosis, osteogenesis, bone defects)	8
Burns	7
Leukaemia	6
Other types of cancer (colorectal, stomach, pancreatic, ovarian, immune system)	6
Articular cartilage damage/defects/lesions	5
Malignant melanoma	3
Neurological malignancies	3
Diabetes	2
Solid tumour cancers	2
Angina pectoris, Chronic wounds, Critical limb ischemia, Crohn's disease, Cutis laxa, Diseases of the eye (Limbal stem cell deficiency), Duchenne muscular dystrophy, Hypoxic-ischemic encephalopathy, Leukodystrophy (Metachromatic), Limbal stem cell deficiency, Minimal change glomerulopathy, Multiple sclerosis, Scars, Spinal cord injury, Systemic lupus erythematosus, Urethral strictures, and Primary Immunodeficiencies (Wiskott-Aldrich syndrome and ADA SCID)	17 (1 per indication)
Total	83

Indication reflecting ICD-11 categories. 80 products categorised, some of which target more than one indication (i.e., burns and chronic wounds)

Source: Authors' elaboration based on collected data

See Annex 4 for: Survey responses on HE-ATMPs' therapeutic indications

3.2. Lessons learned: Identified good practices in Member States

While national regulations for HE products vary across jurisdictions, certain good practices can be identified to support a more effective framework for HE use.

Table 16 – Identified good practices in Member States

Good practice	Description
Reviewing the definition of non-routine to accommodate the access of patients to innovative therapies (EE)	In response to the restrictive 10-patient limit, which may make investments unfeasible for manufacturers, Estonia's NCA has proposed removing this limit and other related restrictions. This aligns with the approach of the Netherlands, which allows for exceptions in some cases, despite setting the same limit.

Good practice	Description
Making information on HE-ATMPs (BE, ES, EE, FI, DE) or the list of eligible HE approval holders (FR, PL, SI) publicly available	In addition to the national provisions regulating the HE, several countries have dedicated websites with information on HE products available. The information may include product name, HE approval holder, date of approval, and in some countries also summary of product characteristics (SmPC), and patient information leaflet (PIL). Some countries make public the list of eligible HE approval holders, such as France (List of Establishments or Organisations Engaged in Activities Related to 'Innovative Therapy Medicinal Products Prepared on an Ad Hoc Basis' [In French]), Poland (Advanced Therapy Medicinal Products Manufacturers Register for Hospital Exemptions [In Polish]), and Slovenia (Register of physicians who use non-routinely prepared advanced therapy medicinal products in their treatment [In Slovenian: currently non-functional, due to legal issues regarding open access]).
Establishing well-structured support mechanisms (IT)	During the application process, support is available from the NCA upon request. Several resources are provided to assist potential HE applicants: an information page accessible on the NCA website, basic support and general advice are provided informally via email, a procedure open to all stakeholders allows for requesting a meeting with the NCA's manager to address uncertainties (e.g., regarding application requirements), and an innovation office is also available to organise innovation meetings upon request.
Setting clear timelines for the application revision (BE)	The timelines of the procedure are described in art. 8, 9 and 10 of the Royal Decree of 08.01.2017[(8)]. It entails a validation phase, an assessment phase and a final decision and publication. All this information, including a diagram on the process, is publicly available in English.
Providing well-defined and precise application data requirements (BE, DE, ES, FR, IT, NL)	These countries have well-defined and structured data requirements for HE applications, covering non-clinical, clinical, and quality data. Applicants must provide extensive evidence on safety, efficacy, and quality, with specific details required. Additionally, applicants need to justify their application with a solid rationale, such as proof of unmet medical need, clinical trial data, or scientific justification. For quality data, compliance with relevant laws (e.g., GMP, quality of starting materials) and oversight by a Qualified Person (QP) are essential.
Establishing regular and clear reporting mechanisms (BE, EE, ES, FI, IE)	Based on the reporting mechanisms described across several countries, these countries stand out as having particularly clear and structured reporting requirements for HE-ATMPs. These countries provide well-defined templates, specific details on the information to be included in reports, and structured timelines for submission.
Providing a cost template for clear and transparent price calculations (ES)	Progressive research incentives, such as Spain's model, where manufacturers can recover part of their investment in innovation, help sustaining the infrastructure required for ATMP production and incentives a transparent price-setting approach.

Source: Authors' elaboration

[(8)] See **Annex 1** – Member State report for Belgium, or visit: https://www.fagg.be/sites/default/files/guidance_atmp-he_1.pdf

4. Conclusions

Hospital Exemption is widely adopted, with 70% of Member States implementing it between 2008 and 2023. Among these the majority (16 out of 19 MS) have, or previously had, HE-ATMPs products available under the HE pathway.

HE primarily serves to address unmet medical need by offering innovative treatments. However, the interpretation of "unmet medical need" varies from country to country. In some countries, national rules allow for a case-by-case assessment to determine whether the HE is the appropriate pathway. In other countries, national rules specify situations when the HE may be utilised, such as: where it is not possible to conduct clinical trials, when a patient is not eligible for or can no longer be enrolled in existing clinical trials, when the product under consideration has no commercial viability, or when there is no alternative treatment available in the market.

Since its introduction, HE-ATMPs have targeted at least 28 therapeutic indications. Information is available for 83 products, reflecting the WHO ICD-11 categories. The most frequent therapeutic indications are viral infections, graft-versus-host disease, osteoarticular disorders, burns, cancer, and articular cartilage damage/defects/lesions.

Currently, it is estimated that 62 HE-ATMPs are available in 13 Member States, with a total of 110 HE-ATMPs approved between 2008 and 2024. The majority are active in Germany (7), France (7) and Spain (5), all countries with a high level of formalisation of requirements. Eight countries have between 1 to 3 available HE- ATMPs (NL, SE, FI, EE, PT, AT, DK, SI). The number of currently available ATMPs includes 24 assumed to be available in Poland and 6 assumed to be available in Lithuania, though these figures are not confirmed. While 21 HE-ATMPs have been approved in Italy, there is no general HE-product approval, instead, there is a specific HE-product use approval for individual patients. Under HE, most available products are Somatic Cell Therapy Medicinal Products are available (37 out of 62), followed by Tissue engineered products (21 out of 62) and Gene Therapy Medicinal Products (4 out of 62).

Some HE approval holders use HE as a bridge towards central marketing authorisation as seen in the following three treatments:

- DE: JERLIX (current name as HE product: NOVOCART Inject), a gel-based matrix-associated cartilage cell product developed by TETEC AG – Status: Under evaluation by EMA's Committee for Medicinal Products for Human Use (CHMP) to obtain a marketing authorisation in the EU. Start of EMA evaluation December 2023, opinion expected for Q3/2025[(9)].

[(9)] Information received from Tetec upon request, on 5 February 2025.

- ES: *ARI-0001* for acute lymphoblastic leukaemia (ALL) in adults and children, developed by the Hospital Clinic de Barcelona. Status: In December 2021, the product was granted eligibility to PRIME [(10)].

- NL: *TIL therapy* for metastatic melanoma, developed by the Netherlands Cancer Institute (NKI) – Status: Start of EMA evaluation expected March 2025[(11)].

Overall, the central marketing authorisation application process may pose challenges for academic manufacturers, as they often lack the necessary resources and expertise to navigate through this application process. **Annex 7** presents the product journey for these three treatments, from early development stages to EMA consideration.

The EMA is supporting academic developers in advancing ATMPs

Besides ARI-0001, a second academic CAR-T cell product, **GD2-CART01 from Ospedale Pediatrico Bambino Gesù (IT)**, achieved PRIME designation in July 2024.Currently, these are the only two academic products included in the EMA PRIME programme[(12)]. This underscores the significant effort required for academic developers to meet the stringent criteria for regulatory support and expedited pathways.

To address these challenges, the **EMA launched a pilot programme in 2022** to support academic and non-profit developers of ATMPs[(13)]. This initiative provides tailored regulatory guidance, assisting academic institutions in navigating the complex authorisation process and ultimately improving patient access to innovative therapies.

Well-defined data requirements and assessment methods provide clarity for HE applicants. In some countries, applicants must provide extensive evidence on safety, efficacy and quality. In other countries, less data may be acceptable regarding safety or efficacy, as long as quality standards are maintained, and the justification is provided. Additionally, applicants must explain why HE is the appropriate pathway, substantiating the unmet medical need. These requirements are aimed at ensuring the safe use of the product and its benefits for the patient.

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(10) More information available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines

(11) Information received from NKI upon request, on 2 February 2025.

(12) For details, please see the EMA list of medicines currently in PRIME scheme, available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines

(13) More information available at: https://www.ema.europa.eu/en/news/ema-pilot-offers-enhanced-support-academic-and-non-profit-developers-advanced-therapy-medicinal-products

HE-ATMPs are produced in GMP-compliant facilities. Although GMP compliance is mandatory for HE-ATMP development, stakeholders highlight the associated costs as a significant challenge, particularly for academic institutions and small-scale developers.

University hospitals and academic medical centres play an important role in expanding HE-ATMP treatment options. Half of the HE approval holders are university or public hospitals - out of the 51 approval holders identified in this study, 26 were public or university hospitals. Other types of organisations include companies (N=14), non-profit institutions (e.g. blood establishments), research centres (N=10) and private hospitals (N=1).

Academic research centres support providing patients access to ATMPs, and HE has provided them with new opportunities, including translating laboratory f discoveries into new clinical therapies and creating biotech spin-offs such as Novadip (BE), PolTREG (PL) and Obnitix (DE). In some cases, public organisations have been instrumental in maintaining the availability of innovative therapies, such as Strimvelis (IT). Additionally, new approaches for university hospitals to engage with the pharmaceutical industry have emerged such as private-public partnerships, exemplified by the establishment of TERAFRONT (ES).

Clear reporting mechanisms enhance transparency and accountability. Mandatory and well-defined reporting mechanisms for approval holders on HE activities and outcomes – provided that specific guidance is available – improve oversight of HE-ATMPs and facilitate knowledge-sharing among NCAs and developers.

Public HE-ATMP approval repositories could support awareness among relevant stakeholders, by making information accessible to patients and physicians. However, this is currently common practice in only a few countries. Additionally, clinical data registries, such as those maintained by the European Society for Blood and Marrow Transplantation (EBMT)[(14)] for CAR T-cell therapies, serve as valuable resources for tracking the development, use, and outcomes of certain products in terms of effectiveness, safety and clinical benefits, although they do not capture the full spectrum of ATMPs.

Networks of European academic institutions could promote knowledge sharing and innovation. In line with this, some manufacturers support the idea of a broad European network to help streamline ATMP manufacturing processes and facilitate the sharing of good practises across different centres. Several HE-

[(14)] This registry has been developed for and by transplant professionals and has a history of over 50 years. It includes data on HE products, which allowed them to compile data on the use of mesenchymal stromal cells (MSCs) in Steroid-Refractory Acute GvHD for the first time. This data demonstrated a survival benefit for responding patients, showing that MSCs produced in academia are a viable treatment option for Steroid-Refractory Acute GvHD.

ATMP manufacturers are part of national or European networks of academic developers where aspects related to ATMP development are discussed and information is exchanged. This may cover a variety of topics, including experiences and knowledge of new technologies, questions related to the costs and financing of ATMPs and regulatory questions.

Adopting good practices can enhance hospital exemption implementation across Europe. Effective implementation of the Hospital Exemption relies on well-defined national regulatory frameworks, transparent processes, and proactive oversight by NCAs.

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Annex 1. Member State Reports

This Annex is provided as a separate document.

It can be found under the link: https://data.europa.eu/doi/10.2925/6354066

Annex 2. Jurisdictions Abroad

This Annex is provided as a separate document.

It can be found under the link: https://data.europa.eu/doi/10.2925/6131679

Annex 3. Survey questions and participation

Introduction

Following the recent event **"Implementation of the Hospital Exemption in the EU and its Role in Boosting Innovation and Patient Access to Innovative Therapies"** held on 21 November 2024, we are launching this survey to gather public feedback on key takeaways related to the implementation of HE across Member States.

This survey aims to explore best practices identified during the event, validating their relevance and assessing their impact in different countries. The study focuses on practices that can support ATMP developers, foster innovation, and improve patient access.

We welcome opinions from diverse stakeholders, whether the practices are implemented in your country or not. The survey is designed to ensure that the final report reflects a comprehensive understanding of HE practices across Member States and provides meaningful insights for the ATMP community.

The aim of the survey is:

- To get feedback from participants of the event “Implementation of the Hospital Exemption in the EU and its Role in Boosting Innovation and Patient Access to Innovative Therapies” on the best practices regarding the current implementation of HE in the EU.
- To investigate whether there are other best practices that should be shared to support national regulators and ATMP developers.
- To understand the impact of these best practices on enabling patient access to ATMPs and boosting innovation around ATMPs.

The survey is anonymous; no personal or identifying information will be collected.

Deadline: 17 January 2025

Section 1: Profile

This section collects basic information to understand the diversity of perspectives contributing to the survey.

1. **Which country are you responding from?** *(Dropdown menu with all EU Member States + "Other")*
2. **Which category best describes your organisation?**

    - Academia
    - Non-profit research organisation
    - Biotech SME (micro-small, or medium-sized enterprise)
    - Large pharma company
    - Scientific society
    - Contract research organisation
    - Contract manufacturing organisation
    - National Competent Authority (NCA)

- Healthcare professional
- Patient organisation or advocacy group
- Healthcare provider (e.g., hospital, pharmacy)
- Funding body (Public payer or social health insurance)
- Regulatory/public authority (other than NCAs)
- Citizen/public
- Other (please specify)

3. **Are you directly involved in HE-related activities (e.g., research, development, regulation, use or reimbursement of HE products)?**
   - Yes
     - If you are involved in HE-ATMP development, which type of Advanced Therapy Medicinal Product (ATMP) are you developing/have you developed?
       - Gene therapy medicinal products (GTMP)
       - Somatic cell therapy medicinal products (sCTMP)
       - Tissue engineered products (TEP)
       - Combined ATMPs
       - Im not involved in HE-ATMP development
   - No

Section 2: Validation of best practices

This section explores best practices identified during the event, assessing their relevance and impact across Member States.

Best practice: Publication of HE approvals and nationwide registry of HE-ATMPs

4. **Are there clear reporting mechanisms regarding the use of HE-ATMPs in your country?**
   - Yes – *Please specify (Open text)*
   - No – *Why not? (Open text)*
5. **To what extent do you think having a registry of HE-ATMPs at national level is a best practice?**
   - 1: Not a good practice – *Open text for comments*
   - 2: Somewhat useful but not essential – *Open text for comments*
   - 3: Neutral/Neither good nor bad – *Open text for comments*
   - 4: A useful practice – *Open text for comments*
   - 5: An essential best practice – *Open text for comments*
6. **Is information on HE-approvals published in your country?**
   - Yes – *Please specify which data are published. (Open text)*

- ☐ No – *Why are the data are not/cannot be published in your country (e.g., national restrictions). (Open text)*

7. **Do you believe that clinical data registries, such as those maintained by the European Society for Blood and Marrow Transplantation (EBMT), could be a useful tool for collecting HE-related data, particularly considering the specific applications for HE presented during the event?**
   - ☐ Yes – *Please provide examples of how the EBMT registry or other (national) registries are or could be used to collect HE data. (Open text)*
   - ☐ No – *Why do you believe such registries are not useful or feasible? (Open text)*
   - ☐ Not sure – *Please elaborate on any additional information or support you would need to assess their usefulness. (Open text)*

Best practice: Consistency among reimbursement possibilities

8. **To what extent do you think the same pricing and reimbursement rules should apply to HE-ATMP and centrally authorised ATMPs?**
   - ☐ 1: Not a good practice – *Open text for comments*
   - ☐ 2: Somewhat useful but not essential – *Open text for comments*
   - ☐ 3: Neutral/Neither good nor bad – *Open text for comments*
   - ☐ 4: A useful practice – *Open text for comments*
   - ☐ 5: An essential best practice – *Open text for comments*
9. **Is national reimbursement of HE-ATMPs a possibility in your country?**
   - ☐ Yes – *What reimbursement mechanisms are in place? (Open text)*
   - ☐ No – *What challenges restrict reimbursement in your country? (Open text)*

Best practice: Pursuing Central Marketing Authorisation

10. **To what extent do you think pursuing a central marketing authorisation as the end goal to HE-ATMPs is a best practice?**
    - ☐ 1: Not a good practice – *Open text for comments*
    - ☐ 2: Somewhat useful but not essential – *Open text for comments*
    - ☐ 3: Neutral/Neither good nor bad – *Open text for comments*
    - ☐ 4: A useful practice – *Open text for comments*
    - ☐ 5: An essential best practice – *Open text for comments*
11. **Would support mechanisms make the central marketing authorisation process more accessible for HE-ATMP developers?** *(Select all that apply and provide feedback on your experience, if any)*
    - ☐ EMA pilot for academic developers of ATMP
    - ☐ EMA Innovation Task Force briefing meetings
    - ☐ National Innovation meetings
    - ☐ EMA Scientific Advice
    - ☐ National Scientific Advice

- ☐ Simultaneous National Scientific Advice (SNSA)
- ☐ EMA Qualification of novel methodologies and biomarkers
- ☐ EMA Prime scheme
- ☐ CAT classification
- ☐ EMA Academia Briefing meetings
- ☐ Parallel EMA-HTA body scientific advice
- ☐ CAT certification
- ☐ EMA SME Office
- ☐ Orphan designation

12. **Is a central marketing authorisation pursued by ATMP developers after making a HE-ATMP available to patients in your country?**
    - ☐ Yes – *To what extent is a central marketing authorisation pursued (e.g., number of HE-ATMPs, specific circumstances)? (Open text)*
    - ☐ No – *What challenges prevent HE-ATMP developers/approval holders from pursuing central marketing authorisation in your country? (Open text)*

Section 3: Success stories of using HE

This section highlights real-world applications of HE to inspire discussion of its potential across Member States.

13. **In Sweden, burn care provides an example of HE is being used for life-saving treatments (e.g., cultured autologous keratinocytes for severe burns). Are there similar cases in your country?**
    - ☐ Yes – *Please specify the cases in your country.*
    - ☐ No – *Please specify possible reasons why there are no similar cases in your country.*

14. **In Belgium, HE has been instrumental in boosting a spin-off company by facilitating early-stage innovation and product access. Are there examples in your country where HE has supported the development of spin-offs or similar initiatives?**
    - ☐ Yes – *Please provide details of the spin-off or initiative and the role of HE. (Open text)*
    - ☐ No – *Please specify possible reasons why there are no similar cases in your country. (Open text)*

15. **In France, the new provision (II of Article L.4211-9-1) regulates the preparation, distribution, and administration of MTI-PP (HE-ATMP) within hospitals as part of the same medical intervention as the tissue or autologous cell collection. Are there examples in your country where a similar provision has facilitated patient access to advanced therapies or supported innovation in hospital settings?**
    - ☐ Yes – *Please provide details of cases where a similar provision has been applied and its impact on patient care or innovation in hospitals. (Open text)*

- No – *Please specify possible reasons why there are no similar cases in your country. (Open text)*

16. **Various Member States have notable examples of a non-profit organisation that holds manufacturing and distribution rights for an approved ATMP, showcasing the potential of public/non-profit ownership of ATMPs. How do you view public or non-profit ownership of ATMPs, and are there similar cases in your country?**
    - **Yes** – *Please provide details of similar cases in your country and share your views on public/non-profit ownership of ATMPs. (Open text)*
    - **No** – *Please share your thoughts on public/non-profit ownership of ATMPs and possible reasons why there are no similar cases in your country. (Open text)*

Section 4: Final comments

This section invites participants to share any additional thoughts or suggestions to ensure no important topics are overlooked.

17. **Are there any additional aspects or insights related to the Hospital Exemption context that were not covered in this survey, or do you have any final comments or suggestions regarding HE practices?** *(Open text)*

Thank you for your participation

Thank you for taking the time to complete this survey. Your insights and perspectives will be carefully considered as part of the study team's efforts to compile the final report on Hospital Exemption (HE) practices across Member States.

If you have any questions or additional input, please feel free to contact the study team at mrodes@predictby.com.

Thank you once again for your input!

Table A1.1 – Survey respondents by country

Country	Respondents	Country	Respondents
AT	4	**IT**	8
BE	15	**LV**	1
BG	1	**LT**	1
HR	1	**MT**	1
CY	1	**NL**	11
CZ	2	**PL**	7
EE	2	**PT**	4
FI	1	**SI**	3
FR	10	**ES**	23
DE	11	**SE**	3
GR	1	**Other***	7
IE	1		

*Other including: EU (x2), Nordic Denmark, Norway, Finland, Sweden (x1), UK (x1)

Source: Authors' elaboration based on survey results

Annex 4. Survey results

Note that respondents were not obliged to answer every question. Therefore, the number of respondents may differ per question.

Survey responses on eligible HE approval holders

Various Member States have notable examples of a non-profit organisation that holds HE approval, showcasing the potential of public/non-profit ownership of ATMPs. Survey respondents broadly supported public or non-profit ownership of HE-ATMPs, particularly for products with limited market potential. For example, in Italy, the non-profit organisation Fondazione Telethon ETS took over the marketing authorisation for Strimvelis, an orphan gene therapy from its original marketing authorisation holder.

Pharmaceutical companies also recognised the critical role academia plays in ATMP research and development, driving innovation. They expressed support for initiatives like the EMA's pilot program to help academic and non-profit developers meet regulatory standards. However, they emphasised the importance of EU legislation ensuring a level playing field, applying consistent scientific and regulatory standards to all similar products, regardless of the producer.

In Belgium, HE has been instrumental in boosting a spin-off company by facilitating early-stage innovation and product access. There are similar cases in other countries, as presented below. Some HE products have been licensed out to private companies instead. In most cases survey responses revealed lack of clarity regarding the existence of spin-offs involved in HE-ATMP due to limited information about HEs issued.

- **BE:** *NVD-003*, currently provided under the HE by Novadip, a spin-off company from Université Catholique de Louvain and St. Luc University Hospital.
- **PL:** *PTG-007*, currently provided under the HE by PolTREG, a spin-off company from the Medical University of Gdansk.
- **DE:** *Obnitix*, developed by the Institute of Transfusion Medicine and Immunohematology and German Red Cross Blood Center Frankfurt am Main and sold to the Company medac who started a multicentre Phase III trial, who is currently providing the treatment under the HE.

In Spain, the establishment of TERAFRONT - a public-private company - aims to facilitate ATMP development by bringing together public institutions and private partners to accelerate research and streamline the transition of innovative therapies from development to clinical use, highlighting the potential of collaborative models to address challenges in ATMP commercialisation and access.

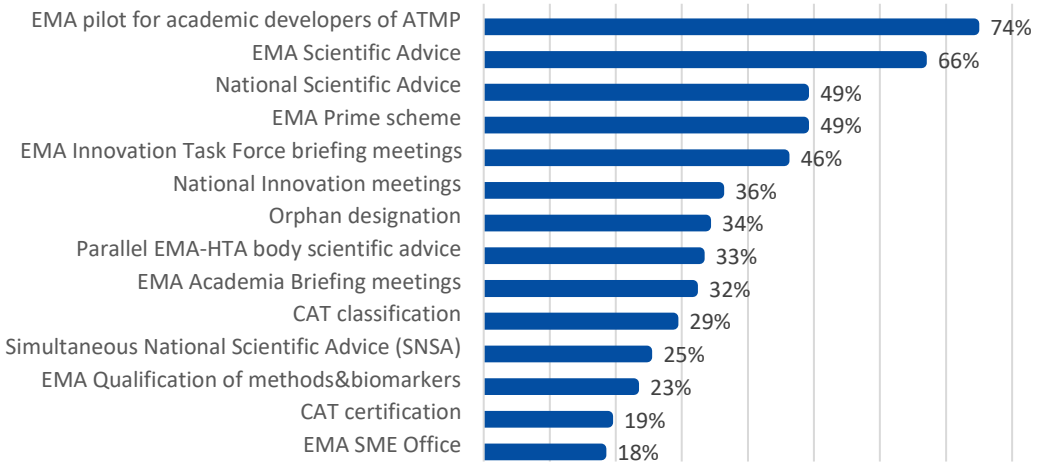
Survey responses on pursuing Central Marketing Authorisation

Regarding the question of whether pursuing a Central Marketing Authorisation as the end goal for HE-ATMPs is considered a best practice, the majority of respondents view it positively. A significant portion rated it as either a useful practice (N=46, 40%) or an essential best practice (N=15, 13%). Others were more moderate in their views, with 21% (N=24) considering it somewhat useful but not essential and 12% (N=14) expressing a neutral stance. A smaller minority, 15% (N=17), regarded it as not a good practice. These results reflect a diversity of

opinions, with many recognising central marketing authorisation's as an ultimate objective while also acknowledging the challenges and limitations associated with its pursuit.

- Despite the variation in survey results within all stakeholder groups, an analysis of the comments provided indicate that there is agreement in that HE is often the only viable pathway for ATMPs that are not commercially feasible for industrial production or global supply, such as treatments for rare diseases or small patient populations. HE provides a regulatory framework that ensures patient access to these therapies where commercial development is not possible. While a central marketing authorisation may be an option for some HE-ATMPs, it is typically challenging for academic institutions or hospitals given limited resources, the high costs associated with central marketing authorisation, and the fact that since the indications HE products target are rare, it is not always feasible to conduct CTs (number of patients is too small).
- HE addresses specific medical needs on a non-routine basis, while central marketing authorisation can expand access across the EU, offering more therapeutic options and overcoming national production restrictions. Most pharmaceutical company representatives responding to the survey value HE as a crucial mechanism for providing innovative care where no alternatives exist. They also support encouraging HE-ATMPs with promising clinical outcomes to pursue further development through clinical trials that could enable central marketing authorisation.

Stakeholders were asked which support mechanisms make the central marketing authorisation process more accessible for HE-ATMP developers. For those who replied (N=86), the EMA pilot for academic developers of ATMP and EMA Scientific Advice were identified as the most relevant, while other mechanisms were considered less impactful.



Despite these replies, respondents highlighted the need to consider the financial, regulatory, and infrastructural challenges of these procedures for academic or SME developers. A few respondents highlighted the need to conduct appropriate clinical trials, and a small minority did not agree and instead expressed that I do not expect academic developers to pursue a central marketing authorisation by themselves, but to transfer/agree with companies.

Survey responses on availability of reporting mechanisms

We asked stakeholders whether clear reporting mechanisms exist for the use of HE-ATMPs in their country. Responses were filtered to include only those from NCAs and individuals involved in the development of HE-ATMPs (N=74, 60%). Survey findings align with the information provided in Member State reports, summarised above. The results confirm our findings:

- Countries with reporting mechanisms: Belgium, Czechia, Estonia, Finland, France, Germany, Italy, Portugal, Spain, and Sweden.
- Countries without reporting mechanisms: Austria, Cyprus, Ireland (due to a lack of current HE activity), Poland, and Slovenia.

Survey responses on the use of HE-ATMP registries

The majority of participants view having a registry of HE-ATMPs at the national level as either essential (N=63, 53%) or useful (N=42, 36%). Fewer participants had less positive views (N=13, 11%): some were neutral (N=5), others considered it somewhat useful but not essential (N=5), and a small minority felt it was not a good practice (N=3).

- As highlighted by respondents, a publicly accessible registry listing products under the HE scheme would enhance transparency across Member States, enabling public scrutiny and ensuring alignment with EU legislation.
- Respondents emphasised that national registries should be consolidated and made easily accessible at the EU level (N=17). An EU-level registry would ensure national datasets are centrally accessible, enabling physicians and patients to explore availability across countries. Even some of those who did not rate the registry as essential or useful advocated for an EU-wide approach.
- Neutral respondents highlighted the importance of clarifying reporting requirements and the scope of such registries, as these factors could significantly influence their perceived value.
- Moreover, it was highlighted that registries that collect clinical data would support pharmacovigilance and facilitate the evaluation of HE-ATMPs' safety and efficacy.

Furthermore, clinical data registries, such as those maintained by the European Society for Blood and Marrow Transplantation (EBMT), were overall considered a useful tool for collecting HE-related data (N=69, 61%). A small number felt that this application was not useful (N=6, 5%) and quite a few felt unsure about its usefulness (N=39, 34%).

- According to respondents, these registries offer a structured, scalable, and coherent platform for tracking the development, use, and outcomes of HE-ATMPs (effectiveness, safety and clinical benefits), particularly in rare and complex applications. The EBMT registry was seen as a best practise example of such types of registries.
- It was also noted that a new registry should focus on diseases as a whole, rather than separating registries by product.
- In particular participants from pharmaceutical companies highlighted that considering the expected low volume of patients receiving HE-ATMPs, special attention should be paid to ensure long-term follow-up periods are appropriately risk-based and reflect the level of evidence available including any known and/or potential risks associated with the product.

- Some noted that willingness to join a new registry would depend on requirements and individual case capabilities. Data ownership and any relevant reporting responsibilities would need to be defined.

Participants who believed registries were not useful highlighted concerns about regulatory differences between countries and issues with data ownership and contracts in large registries.

Survey responses on HE-ATMPs' therapeutic indications

As highlighted in the survey, **Sweden** provides an example of HE being used for life-saving treatments, specifically in burn care, where cultured autologous keratinocytes are applied to severe burn patients. To assess whether similar cases exist, survey respondents were asked about comparable uses of HE-ATMPs in their respective countries. The responses aligned with findings from our Member State reports, confirming that **France, Germany, Italy, the Netherlands, Poland,** and **Spain** all report HE-ATMPs for the same or a similar indication.

Annex 5. Template for national implementation reports

Currently, there is no consistent approach to collect data on HE, and levels of transparency vary. The template for national implementation reports serves as a first step towards supporting Member States in developing a structured reporting system, providing preliminary guidance in view of upcoming regulatory requirements. It has been designed to facilitate structured and standardised reporting on the use, safety, and efficacy of HE-ATMPs. However, it is important to note that this template is a preliminary draft and has not yet been reviewed by ATMP developers or NCAs. As such, it should be considered a starting point to guide discussions and the refinement of a final reporting format.

The template aims to support EU Member States in collecting data on HE, while also enabling NCAs to review compliance and contribute to transparent regulatory oversight. The objectives of this template are to:

- Provide a **preliminary structure** for Member States to consider when developing the final reporting template.
- Facilitate the **collection, reporting, and review** of data by NCAs and its subsequent publication in the EMA repository.

Summary overview	
General information	
HE approval date	DD-MM-YYYY
HE approval end date	DD-MM-YYYY (if applicable)
Approval duration (in years)	Formula to calculate approval duration (today or end-date minus approval date) (if applicable)
Justification of use of HE	Description of justification
HE approval holder	Name(s)
Manufacturing location(s)	Name location(s)
Medicinal product details (general)	
Product name	Name
Type of ATMP	Drop-down menu with: (1) somatic-cell therapy medicines (2) gene therapy medicines (3) tissue-engineered medicines (4) combined ATMP
Active substance	Clearly describe the nature of the active substance(s) (e.g. cells, genes, tissues, biologics)
Origin of cells	Drop-down menu with (only applicable to cell/tissue products): (1) autologous (2) allogeneic (3) combination autologous/allogeneic
Administration information	

Administration mode	Drop-down menu with most common types of administration (incl. “other” with open text field)
Frequency and duration of administration	Description of frequency and duration
Strength per dosage unit	Dosage + relevant measure
Treatment information	
Therapeutic indication	Short description of therapeutical indication(s)
Eligibility of patients	Short description of which patients are eligible for the product
Number of patients treated	Formula to add up patients treated (based on patient-related information)
First administration date	
Last administration date	To be left blank in case of single tie treatments.
Number of doses administered	Formula to add up doses administered (based on patient-related information)
Pharmacovigilance reporting	
Number of serious adverse events	Formula to add up number of serious adverse events (based on patient-related information)
Number of adverse reactions	Formula to add up number of adverse reactions (based on patient-related information)
Summary of aggregated reported toxicities	Description of aggregated reported toxicities
Clinical outcome data	
Aggregated results	Conclusion / interpretation of clinical outcome data
Summary of clinical data & laboratory tests	Description of data (incl. for example, biomarkers)
Patient outcomes	Description of outcomes (incl. aggregated patient-reported outcome data)
Post-administration follow-up	Description of post administration safety and efficacy follow-up / monitoring
Planned follow-up duration	In years
Summary of available clinical data	Description of available data
Benefit-risk evaluation	Evaluation and conclusion

Qualitative and quantitative composition of the finished product			
Component	**Description**	**Quantity per dose**	**Function**
Component A			
Component B			
Component C			
Component D			
Component E			
Component F			
Component G			

Information to be reported per patient	
Personal information	
First name	Name
Last name	Name
Sex	Drop down menu: (1) male (2) female
Birthdate	DD-MM-YYYY
Patient identification number	Number
Background information	
Previous treatment(s)	Description of previous treatments
Disease phase at administration	Description of disease phase
Prescribing (healthcare) professional	First and last name
Treatment location	Name of treatment location
Treatment information	
Date(s) of administration	Date(s)
Total # of doses administered	Number
Total dosage administered	Number (in relevant measure)
Total # of batches used	Number
Pharmacovigilance information	
Number of serious adverse events	Number
Date(s) of serious adverse events	Date(s)
Description of serious adverse events	Description of serious adverse events
Number of adverse reactions	Number
Date(s) of adverse reactions	Date(s)
Description of adverse reactions	Description of adverse reactions
Toxicities (type, severity) occurred	Description of toxicities occurred
Clinical outcomes	
Summary of clinical data and laboratory tests	Description (incl. for example, biomarkers)
Patient response	Description of response
Description post administration follow-up activities	Description of follow-up activities
Follow-up duration	Description of duration
Disease relapse(s)	Drop-down: (1) yes (2) no
Disease relapse description	Description of relapse reaction

Information to be reported per manufactured product item	
Patient information	
Patient identification number	Number (related to "patient-related info tab)
Batch information	
Batch identification number/Lot No.	Number
Batch size	Number (in relevant measure)
Origin of cells	Drop-down menu with (only applicable to cell/tissue products): (1) autologous (2) allogeneic (3) combination autologous/allogeneic
Date of production	DD-MM-YYYY
Name of donor centre	Name
Identification number donor centre	Number
Starting materials information	
Type	Description
Lot number	Number
Quality control data	
Results of biological analyses and screening tests	Including for example, sterility and stability
Summary of batch analysis data	
Details on measures and controls of microbiological/viral safety	Description
Deviations	Description of deviations

Annex 6. National provisions regulating the Hospital Exemption

Country	Name of national provision(s) in national language and translation in bold (link available)	Year when the national provision(s) entered into force
AT	Arzneimittelgesetz - paragraph 7(4) and (5) **(Medicinal Products Act)** Gesamte Rechtsvorschrift für Krankenanstalten- und Kuranstaltengesetz **(Federal Act on Hospitals and Health Resorts for considerations concerning health centres)**	2009
BE	Wet op de geneesmiddelen [voor menselijk gebruik] - art. 6 quater, section 3, subparagraph 1, 7° **(Medicines Act [for human use])** Koninklijk besluit betreffende de ziekenhuisvrijstelling voor geneesmiddelen voor geavanceerde therapie (8 Januari, 2017) **(Royal decree on hospital exemption for advanced therapy medicines (January 8, 2017))**	2017
CY	Ο Περί Φαρμάκων Ανθρώπινης Χρήσης (Έλεγχος Ποιότητας, Προμήθειας και Τιμών) Νόμος του 2001 (70(I)/2001) **(Medicines Act for Human Use (Quality, Supply and Price Control) of 2001 (70(I)/2001))**	2010
CZ	UST-37 verze 1 - Zákon o léčivech - Žádost o nemocniční výjimku pro léčivé přípravy moderní terapie **(Act on Pharmaceuticals Section 49(a) and (b))**	2013
DE	Arzneimittelgesetz - section 4(b) **(Medicinal Products Act)**	2009
DK	The manufacturing of HE-ATMPs is regulated as part of the **Compassionate Use** permits: Lægemiddelloven - section 4(a) and section 29 **(Medicines Act)** Vævsloven - section 11(a) **(Tissue Act)**	2008
EE	Ravimiseadus - paragraph 16 **(Medicines Act)** Haiglaerandi ravimi loa taotlemise tingimused **(Conditions for applying for a hospital exemption medicine approval)**	2022
ES	Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial **(Royal Decree 477/2014)**	2014
FI	Lääkelaki 15 c § (16.10.2009/773) - section 15(c) **(Medicines Act)**	2009
FR	Code de la santé publique (CSP) - L. 4211-9-1; L. 5121-1 (17°); R. 4211-34; R. 4211-43; R. 5121-210; R. 5121-214 **(Public Health Code)** Arrêté du 4 février 2013 **(Order of 4 February 2013)**	2013

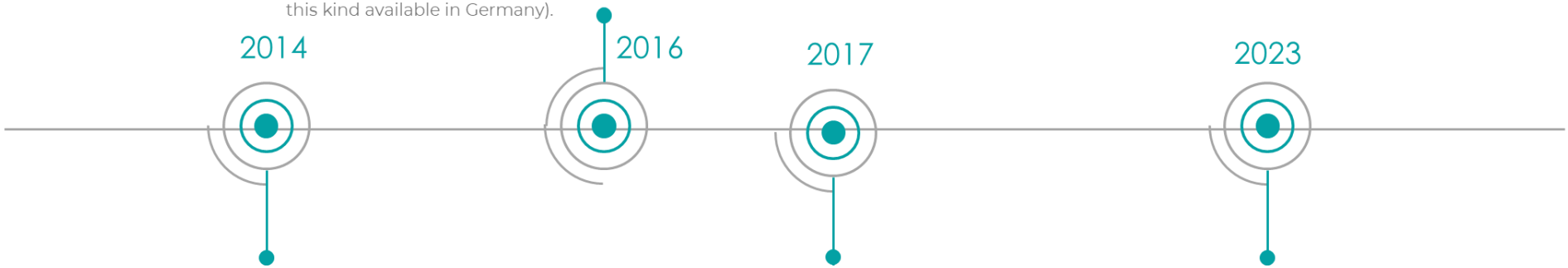
Country	Name of national provision(s) in national language and translation in bold (link available)	Year when the national provision(s) entered into force
IE	The Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) Medicinal products (control of placing on the market) regulations 2007 (amendment) regulations 2009 S.I. No. 3 2009)	2009
IT	Decreto Ministero della Salute - Articles 1-10 including attachments **(Ministerial Order by the Ministry of Health)**	2015
LT	Farmacijos įstatymas - chapter 8.9 **(Pharmaceutical Act)** Lietuvos Respublikos sveikatos apsaugos ministro įsakymas (July 28, 2010, no. V-675) **(Order of the Minister of Health of the Republic of Lithuania (28 July, 2010, no. V-675)**	2010
MT	**Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations for Medicinal Products for Human Use** *While the guidelines establish the foundational considerations for HE, they do not provide extensive details on all core elements of the legislative framework.*	2023
NL	Geneesmiddelenwet - Article 40(3)(d) **(Medicines Act)**	2009
PL	Ustawa z dnia 6 września 2001 r. prawo farmaceutyczne – Article 2(33)(b), 3(7), and 38(a), 38(aa) and 38(ab) **(Pharmaceutical Act of 6 September 2001)**	2011
PT	Portaria n.º 138/2014, de 7 de julho **(Ordinance No. 138/2014 of 7 July)**	2014
SE	Läkemedelslag (2015:315) – chapter 3(5) **(Medicines Act (2015:315)** Läkemedelsverkets föreskrifter (LVFS 2011:3) om läkemedel som omfattas av sjukhusundantaget **(The Swedish Medicines Agency's regulations (LVFS 2011:3) on medicinal products covered by the hospital exemption)**	2011
SI	Zakon o zdravilih (zzdr-2) - chapter 5 **(Medicinal Products Act (MPA-2)**	Not identified

Source: Authors' elaboration based on website search

Annex 7. Product journeys towards central marketing authorisation

Gel-based matrix-associated cartilage cell product

After the experience gained by the company, TETEC AG developed **Novocart Inject**, another tissue-engineered product (as an injection preparation), which was approved as an HE-ATMP by the PEI in **June 2016** (initial approval until 2029).
The product is intended to treat circumscribed 3rd and 4th degree articular cartilage damage in the knee, particularly in defects with preserved containment (i.e., a completely preserved cartilage rim surrounding the defect). It offers a minimally invasive approach (arthroscopy or mini-arthrotomy) by means of a double-chamber syringe (only product of this kind available in Germany).

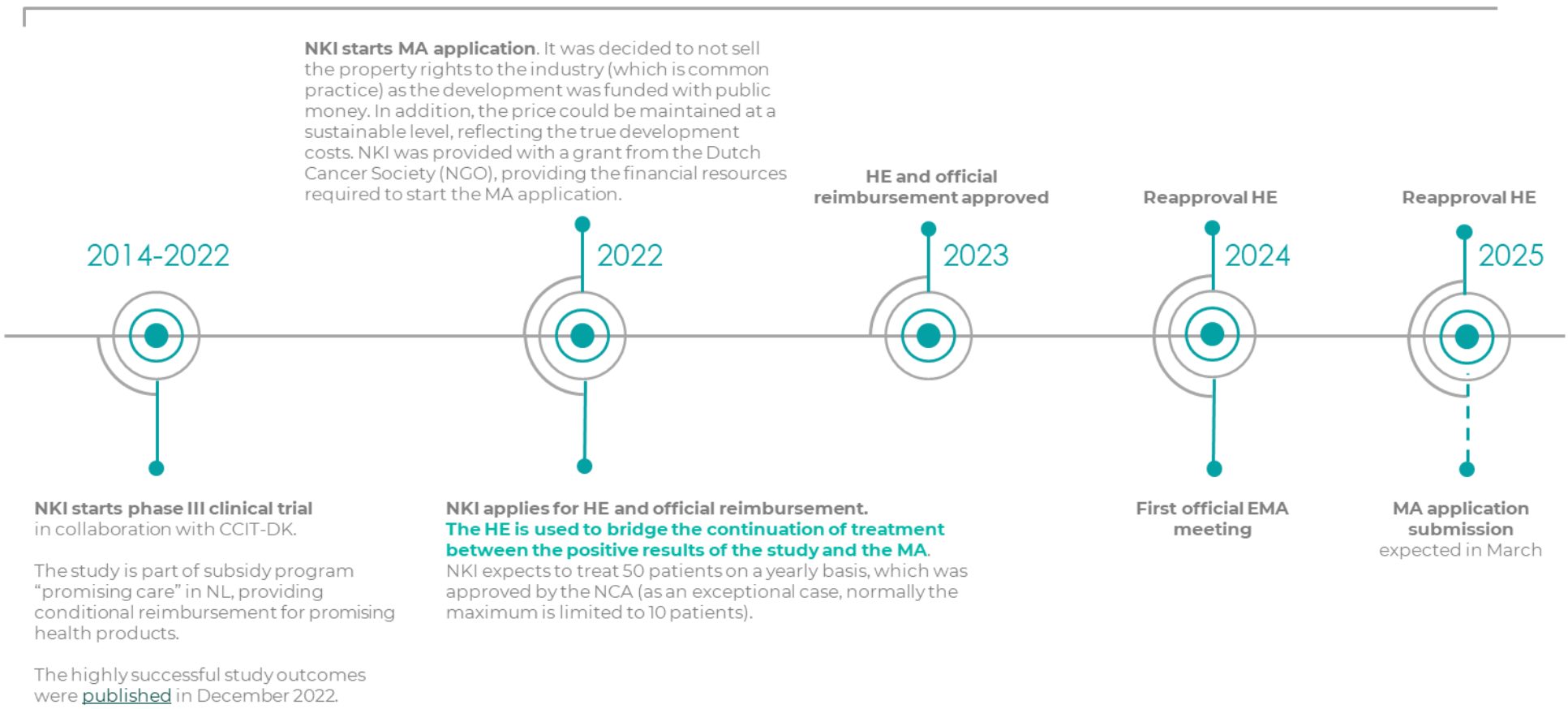


In November 2014, TETEC AG, a biopharmaceutical company, active in the field of cartilage cell therapies, ATMPs and suitable biomaterials, obtained the approval for manufacturing **Novocart 3D** (matrix for implantation) under the HE in Germany. This Tissue-engineered product is indicated to treat full-thickness cartilage damage of the knee joint of 3rd and 4th degree caused by acute or repeated trauma or by osteochondrosis dissecans.

The approval of **Novocart 3D** was **renewed** in **September 2017**. The company used the HE pathway as a means of providing treatment options for patients whose condition does not adequately respond to conservative treatment. At the same time, the company aimed to continue gathering evidence to support a future application for a Central Marketing Authorisation with the EMA.

As a result of the experience with HE-ATMPs in Germany, and the continuous evidence retrieved throughout the treatment processes, TETEC AG announced in 2023 that it had submitted a Marketing Authorisation Application (MAA) for a **gel-based matrix associated cartilage cell product**. At the time of the data collection (2024), EMA was still evaluating the application.

TM001 (TIL Therapy)



NKI starts MA application. It was decided to not sell the property rights to the industry (which is common practice) as the development was funded with public money. In addition, the price could be maintained at a sustainable level, reflecting the true development costs. NKI was provided with a grant from the Dutch Cancer Society (NGO), providing the financial resources required to start the MA application.

NKI starts phase III clinical trial in collaboration with CCIT-DK.

The study is part of subsidy program "promising care" in NL, providing conditional reimbursement for promising health products.

The highly successful study outcomes were published in December 2022.

NKI applies for HE and official reimbursement.
The HE is used to bridge the continuation of treatment between the positive results of the study and the MA.
NKI expects to treat 50 patients on a yearly basis, which was approved by the NCA (as an exceptional case, normally the maximum is limited to 10 patients).

First official EMA meeting

MA application submission expected in March

ARI-0001

1990

Research experience with A3B1, a monoclonal antibody developed by the HCB

2013-2017

Lab work for CAR-T begins and preclinical experiments take place: One of the main goals pursued with the CAR-T Unit is to bring this treatment closer to patients who had few therapeutic options, thus expanding the options for treating tumors and offering patients good treatment alternatives.

2017-2019

CART19-BE-01 trial (NCT03144583) takes place, with 27 patients treated with ARI-0001. **After obtaining positive results, the CAR-T Unit considered pursuing a Centralised Marketing Authorisation** – however, the process proved challenging and it was decided to request HE approval at the NCA first.

2019-2021

Compassionate use: After the first Clinical Trial, and while submitting an application for HE to the Spanish NCA, AEMPS, ARI-0001 was used via compassionate use in 8-10 patients.

2021

HE Approval is granted: ARI-001 becomes the second HE product approved by the NCA, becoming. the first treatment with genetically modified cells and fully developed in Europe that was approved by a regulatory agency. For this specific product, **there was an informal condition that HCB would try to obtain an MA for this product.**

2022

PRIME designation: ARI-0001 is **designated as "PRIME" (Priority Medicine in Europe) by the European Medicines Agency (EMA)** for adult patients with acute lymphoblastic leukaemia. End goal is obtaining Centralised Marketing Authorisation.

2022-2023

CART19-BE-02 trial (NCT04778579) takes place, with 32 patients treated with ARI-0001.

2024

Preparing application for extension of HE approval.: This extension may last up to 5 years. At this moment 30-35 patients have been treated with the product under the HE pathway.

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