AGENZIA ITALIANA DEL FARMACO

Hospital Exemption

Non repetitive use of Advanced Therapy Medicines

Sandra Petraglia

Translating Innovation into access for ATMPs

3rd EU-Innovation Network multi-stakeholder meeting

Rome

November 15th 2024

Hospital exemption

Accelerator of innovation

...or obstacle to innovation?

This unique legal instrument represents a regulated pathway for accessing ATMPs under conditions overseen by national medicine regulatory agencies... for some unmet medical needs, HE is the only pathway for access to innovative medicines

ISCT Committee Paper
N. Cuende et al. / Cytotherapy 24 (2022) 686690

What type of ATMP?

Types of ATMP

- Mesenchymal stromal cell
- Hematopoietic stem cells
- Lymphocytes
- Dendritic cells
- Autologous EGFR activated NK Cells
- Gene therapy (CD34+)
- Allogenic/Autologous CD19/GD2/CD7-CART
- CARCIK-CD19

Indications

Mainly immunological and haemato-oncological

Increasing range of clinical conditions

Potential for clinical development

Generally not part of regulatory assessment by MSs

Scale of manufacturing*

- Less than 10 batches
- Less than 50 batches
- 50-200 batches
- More than 200 batches
- Patient exposure from a minimum of 336 to a maximum of 1600

** Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries G.M. Coppens et al. Cytotherapy 22(2020) 592-600*

What type of ATMP?

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Art. 28

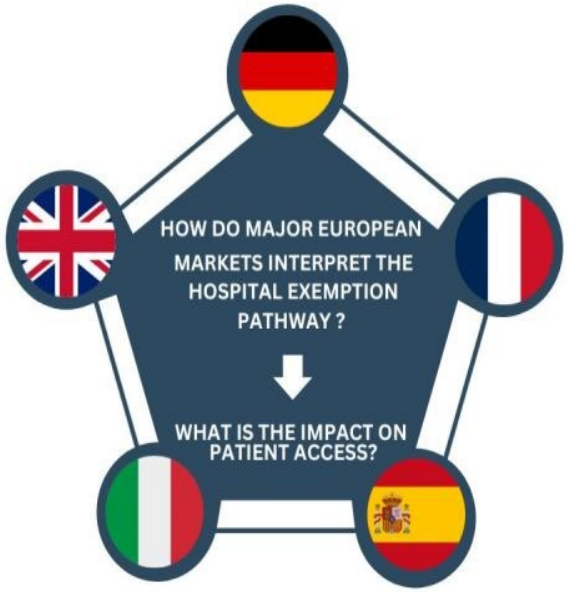
- Prepared on a non-routine basis
- Specific quality standards
- Used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner
- Individual medical prescription
- Custom-made product for an individual patient
- Manufacturing authorized by the competent authority of the Member State
- National traceability
- Pharmacovigilance requirements

Different implementations across MSs

- Duration of the HE license (limited n. of years in 4 out of 9 MS)
- Facilities that may administer ATMP-HE (restricted to hospitals and public institutions in only 3 of 9 MS)
- Official guidance on the requirements for "custom made"
- Number of patients that can be treated
- Conditions for access
- Coverage of HE costs

Implementation of HE across four European Union (EU4) countries (France, Germany, Italy and Spain) and the United Kingdom (UK)

https://inbeeo.com/2023/09/21/implementation-and-impact-of-hospital-exemption-pathway-for-atmps/



Variable and additional requirements for HE	France	Germany	Italy	Spain	UK
Organisation responsible for authorisations	ANSM	PEI	AIFA	AEMPS	MHRA
Scope					
Non-routine basis/custom-made product	Non-defined	Guidance	Non-defined	Non-defined	Guidance
Number of patients	Non-defined	Non-defined	Non-defined	Non-defined	Non-defined
Duration of license	5 years	Non-defined	Non-defined	3-5 years	Non-defined
Annual reporting	Required	Required	Required	Required	Required

Difference in interpretation and implementation of the HE pathway across the major European countries on multiple levels:

- Lack of a uniform definition for the term "non-routine basis" leads to a case-by-case basis interpretation
- The lack of harmonisation of HE regulation has led to **divergent motivation for its use** (FR and IT alongside clinical trials for patients that miss the eligible window, DE and ES for data collection towards obtaining a MA via centralized European registration)

- France and Germany do not restrict the type of organizations eligible for licenses, whereas Italy and Spain limit eligibility to hospitals and public institutes, respectively.
- France and Italy restrict licenses if a centrally approved ATMP is already available, while Germany and Spain lack clear restrictions.
- Some countries, as Italy, impose additional requirements, such as evidence of high unmet medical need or requirement of clinical data before issuing the HE licenses.
- Different levels of evidence on efficacy and safety

All countries require **quality standard** for ATMP manufacturing process

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Annual reporting	Required	Required	Required	Required	Required
Eligibility					
Eligible license holders	Unrestricted*	Unrestricted	Public institutes	Hospitals only	Unrestricted
Restricted when licensed ATMPs are available	Yes**	No	Yes	No	No
Medical need considerations	Yes**	No	Yes	No	No

https://inbeeo.com/2023/09/21/implementation-and-impact-of-hospital-exemption-pathway-for-atmps/

The absence of a definition for "non-routine basis" should be regarded as a deliberate omission by the EU regulator which enables the EU member states to make interpretations in the context of each specific healthcare system

Pachocki J and Verter F (2024) Polish regulatory system regarding ATMP hospital exemptions. Front. Immunol. 15:1379134. doi: 10.3389/fimmu.2024.1379134

- Lack of adequate evidence from clinical trials
- Expected clinical benefit
- Risks associated with achieving this benefit justified in the light of the current state of knowledge and consistent with the ethical principles of the medical profession.

Ethical Considerations for the Application of the HE Pathway

- Balance needed between unmet medical need and scientific uncertainty
- Balance needed between access to innovative products with no commercial interest and large scale access to marketed innovative products
- Transparency on HE applications across the EU and the related evidence
- HE may prevent unethical medical tourism or direct-to-consumer exploitation
- Competition with ongoing clinical trials in the same indication to be avoided

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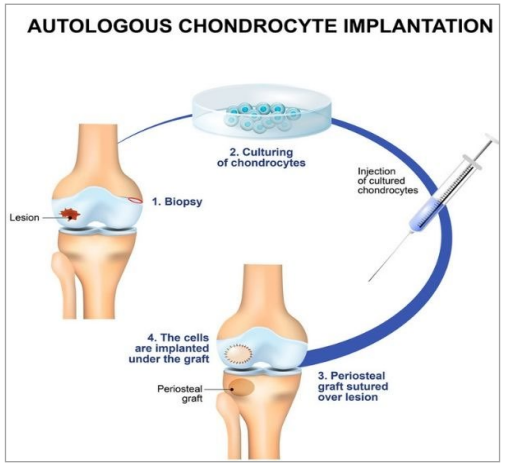
Hospital Exemption and Access to Centrally Approved ATMPs

- In principle, HE ATMPs addresses the need of patients when centrally approved ATMPs are either not available, or not commercially feasible. However, in case of a central application for an ATMP, with the same or similar indication in which a HE product already exists, the situation can become an uneven playing field.

- There are few examples where centrally approved ATMPs faced challenges due to availability of similar HE ATMPs at local level.

One example is ChondroCelect®, a tissue engineered product indicated to treat symptomatic cartilage defects. Despite being the first EMA approved in 2009, it faced delays before successfully entering the EU market, due to market acceptance and reimbursement negotiations.

ChondroCelect® was withdrawn from the EU market in 2016 for commercial reasons.
One commercial reason was related to the presence of other chondrocyte products in Germany operating under the HE.



Hospital Exemption undermines the development of Centrally Approved ATMPs?

Stringent requirements for ATMPs

↓

High development and production costs

Consequences of costs and national policies on multinational development of centrally authorised ATMPs and access to ATMPs

HE has different requirements across MSs as concerns quality control criteria

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Reduction in production costs

Disincentive to development of centrally authorised ATMPs if used as benchmark for price determination or if licensed for use with reduced regulatory requirements

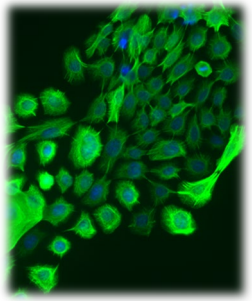
↓

Incentive to innovation if ideally managed to cover unmet need and at the same time stimulate research

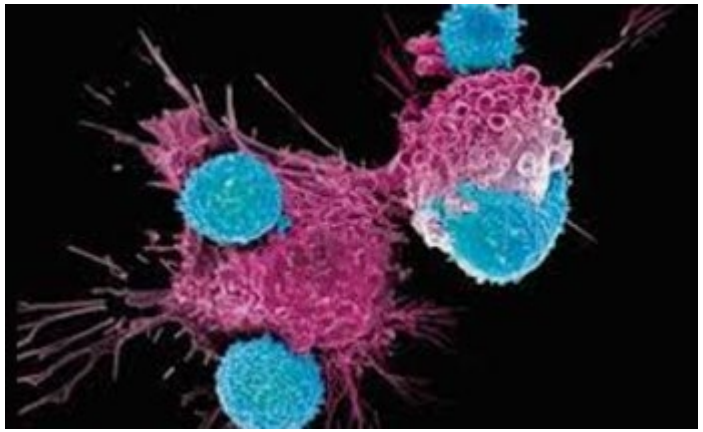
Hospital exemption - Italy

- Number of applications for 2023: 38
- Overall applications since 2015: 332
- Overall applicants: 20
- Facilities: 9

Mainly immunological and haemato-oncological setting



No mandatory requirement of previous clinical trials – however, scientific evidence and expected clinical benefit rationale are required



New indications requested:

- Neuroblastoma (CAR-T)*
- Retinoblastoma (CAR-T)*
- Glioblastoma
- Glioma (CAR-T)*
- Melanoma (dendritic cells)
- Osteosarcoma (CAR-T)
- Lupus erythematosus (CAR-T)
- Dermatomyositis (CAR-T)
- ARDS associated to COVID-19 (mesenchimal stromal cells)
- Vestibular fistula
- Neuronal damage

* 38 applications until September 2024

New clinical trials after HE: 3

In conclusion

HE use varies significantly across member states depending on:

- ✓ national legal implementation,
- ✓ local policy makers interpretations,
- ✓ clarity of guidance at the national level,
- ✓ reimbursement opportunities and
- ✓ the level of ATMP research and development activities carried out by domestic academic and commercial organizations.

Stakeholders should work together:

- ➢ *to create a system where the use of the HE pathway is focused on filling gaps where commercial ATMPs are lacking and on stimulating research and innovation also through collaborative approaches*
- ➢ *towards harmonising its application and interpretation across Europe to ensure sustainable and equal access to safe and potentially lifesaving treatments and support innovation. The Pharma revision can be a powerful tool in this respect.*

HaDEA and DG SANTE

AGENZIA ITALIANA DEL FARMACO

Study on Hospital Exemption in relation to the implementation of the Advanced Therapy Medicinal Products (ATMP) Regulation (EC) No. 1394/2007

HaDEA and DG SANTE

Study context & interview	Different interpretations of the ATMP regulation have yielded in variable Hospital Exemption (HE) national rules and implementation outcomes. In this context, the collection of evidence on the implementation and functioning of the HE in EU Member States through a dedicated study will shed light on the role of the HE along the pathway of ATMPs, from basic research and pre-clinical studies to the conduct of clinical trials and product development up to their delivery from the healthcare systems. In the previous stage of the study, we performed an initial in-depth search and exploratory interviews, collecting all available information on HE from the official channels. Now, the aim of this interview is to complement the information collected so far. This guide consists of three different parts. Part I presents preliminary questions and interview set-up. In Part II we introduce the list of indicators we have developed and ask questions to understand how HE is implemented in your country. Part III covers final HE-related questions and closing remarks. The overall aim of this study is to map the situation in all Member States and identify best practices and recommendations. The direct insights from this interview will be shared with HaDEA and DG SANTE only. The final report of this study is expected to be published in 2024, but the information you share here today will be kept confidential.