

Hospital Exemption for Advanced Therapy Medicinal Products (ATMPs): greater transparency needed in order to improve patient safety and access to ATMPs

Executive Summary

In Europe, Advanced Therapy Medicinal Products (ATMPs) comprise gene therapy medical products (GTMPs), somatic cell therapy medical products (CTMPs), tissue engineered products (TEPs) and combined ATMPs. Governed by Regulation (EC) No 1394/2007 (the “ATMP Regulation”) of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, all ATMPs in the EU are required to obtain a marketing authorisation (MA) via the centralised procedure, with the exception of those falling under Article 3(7) of Directive 2001/83/EC, the so-called ‘hospital exemption’ (HE).

Article 3(7) of Directive 2001/83/EC allows manufacturing of products falling under the HE to be authorised at national level, leaving it to Member States to define HE requirements within their national legal frameworks. Though Article 3(7) of the Directive specifies as compulsory for exempted ATMPs that national traceability and pharmacovigilance requirements as well as the specific quality standards be equivalent to those provided for at Community level, this approach has led to differences in the way the HE has been interpreted and implemented across the EU. These differences have created parallel paths to market access for ATMPs, resulting in uncertainty and barriers to patient access, transparency, and incentives for developing ATMPs in the EU.

EBE and EFPIA call on the European Commission to improve patient safety and access to effective therapies in the field of ATMPs through two actions:

1. Development of a ‘best practice guide’ on national implementation of hospital exemptions for ATMPs.
2. With the support of national competent authorities, development of a register of all ATMPs made available under HE.

This would improve transparency on HE products for all interested parties, informing:

- Patients on potentially available treatment options,
- Health care providers on potential treatment options for their patients as well as safety and efficacy on such treatments,
- National competent authorities on situations where other treatments exist for indications for which an HE has been requested as well as demonstrating regulatory oversight,
- Manufacturers and developers of ATMPs on unmet medical need where fully authorised products are needed as well as relevant clinical experience.

With the above actions we would better protect patients, incentivise development of ATMP products and promote broad patient access to these novel therapies across EU.



Table of Contents

1. Issue	2
2. Considerations	3
Why greater clarity and convergence is needed: call for a common best practice guide.....	3
Why is greater transparency needed?.....	4
<i>A central, publicly available repository of all the products across all EU member states should be established</i>	4
<i>Increase knowledge on efficacy and adverse reactions for ATMPs available under hospital exemption</i>	4
3. Conclusion and Call to Actions	5

1. Issue

In Europe, Advanced Therapy Medicinal Products (ATMPs) comprise gene therapy medical products (GTMPs), somatic cell therapy medical products (CTMPs), tissue engineered products (TEPs) and combined ATMPs. ATMPs of the same class can be very different [e.g. autologous (the medicinal product contains cells or tissues coming from the patient himself) versus allogeneic (coming from another human being)], simple versus complex gene constructs. Due to the novelty, complexity of the manufacturing process and technical specificity of ATMPs, specially tailored and harmonised rules are needed to authorise their use, to ensure the free movement of ATMPs within the European Union (EU), improve patient access across the EU and ensure the effective operation of the EU internal market in the biotechnology sector. These specific rules were set up by the Regulation (EC) No 1394/2007 (the “ATMP Regulation”) of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products.

All ATMPs in the EU are required to obtain a marketing authorisation (MA) via the centralised procedure, with the exception of those falling under Article 3(7) of Directive 2001/83/EC, the so-called ‘hospital exemption’, i.e. ATMPs prepared on a non-routine basis and fulfilling additional specified criteria. The ‘hospital exemption’ (HE) was created under Article 28(2) of the ATMP regulation which amended Article 3 of Directive 2001/83/EC by adding a paragraph 7 that refers to ATMPs *“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, in order to comply with an individual medical prescription for a custom-made product for an individual patient”*. Therefore, and in consideration of recital 6 of the preamble of the Regulation, when an ATMP is not intended to be marketed and not intended to be industrially prepared (non-routine), it is out of the scope of the Directive.

Article 3(7) of Directive 2001/83/EC allows manufacturing of products falling under the HE to be authorised at national level, subject to certain conditions, and leaves it to the Member States to define the HE requirements within their own legal framework. The conditions of Article 3(7) of the Directive specify as compulsory for exempted ATMPs that national traceability and pharmacovigilance requirements as well as the specific quality standards be **equivalent** to those provided for at Community level in respect of ATMPs for which a centralised MA is required. This approach of implementation by the Member States has led to differences in the way the HE has been interpreted and implemented across the EU. These differences have created parallel paths to market access for ATMPs, resulting in uncertainty and barriers to patient access, transparency, and incentives for developing ATMPs in the EU.



HE has a legitimate purpose where there is unmet medical need, for example where no similar centrally authorised ATMP is available for the same indication or where no clinical trial is available in the same Member State, and when applied in a harmonised way across Member States as the legal framework intended. Considering the complexity and diversity of products and the current variety of national frameworks, which potentially leads to undefined pathways, the below paper advocates for two important pillars:

- Greater clarity and convergence on interpretation of HE provision and implementation in national legal systems through creation of a common best practice guidance
- A system that promotes equitable patient access across the EU to ATMPs through greater transparency on the use of HE via:
 - A central repository of all HE products across all Member States
 - Increased knowledge on efficacy and adverse reactions for ATMPs available under HE

2. Considerations

WHY GREATER CLARITY AND CONVERGENCE IS NEEDED: CALL FOR A COMMON BEST PRACTICE GUIDE

The main aim of the ATMP Regulation is to give a robust legislative framework across all EU Member States in order to protect public health, and to foster and incentivise innovative research and biotechnological development in Europe. ATMPs in the EU are required to follow the centralised MA pathway, which enables pan-European access.

The HE is an exemption to the central MA requirement for ATMPs for products prepared on a non-routine basis and used within the same Member State in an hospital, under the sole professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

However, at present, there are divergent approaches and gaps in the implementation of the HE across Member States. For example, as there is no harmonised definition of 'prepared on non-routine basis', there is significant divergence in the interpretation of this principle by the different Member States. For example, some countries define non-routine in quantitative terms (e.g. maximum of 10 patients per year) while other countries prefer a case-by-case approach based on the scale of manufacture and the amount of clinical experience available to assess the product. There are still other countries that have not elaborated a definition of non-routine in their national laws or guidelines on HE.

Another area where different approaches are used between Member States are the eligibility criteria for HE authorisation. In some Member States, HE is limited to cases where there is no available treatment or clinical trial for the patient. Other Member States do not have such limitations, which can lead to a parallel path to patients and even the national market, potentially interfering with recruitment of patients for clinical trials for the same indication. This is especially important in rare diseases, and constitutes an obstacle to investment in innovation.

The complexity of the product and manufacturing processes of an ATMP must also be taken into consideration. For complex ATMPs, such as CAR-T cells and gene-therapy products, HE should be considered with extreme caution since these products require more control during the manufacturing process and small changes can impact patient benefit/risk ratio in a significant way. There is currently no clear and harmonised position across all Member States on application of a risk-based approach toward authorisation to manufacture and use HE products.

A clear and transparent picture of national legal and regulatory requirements for HE and the practical expectations for these products is needed in **every** Member State in order to facilitate an increased awareness of each country's national system of HE, help educate and inform all stakeholders, in the debate on complexity of HE system and further highlight the need for convergence across EU. For example, a webpage managed by the European Commission linking to the requirements on HE and list of HE products on national competent authority websites in all Member States.



European convergence of HE requirements is necessary to ensure confidence in quality, safety and efficacy of all ATMPs across Member States to the benefit of patients. Harmonisation will also ensure standards for quality, traceability and pharmacovigilance equivalent to those at the Community level for centrally authorised ATMPs are in place, as required under Article 28 of the ATMP Regulation.

EBE and EFPIA would welcome a multi-stakeholder dialogue focused on the current state of HE across all Member States. We call for a common best practice guide to Member States for implementation of the HE with the aim to unify approaches across the EU in the interest of patient access and safety, and a functional internal market.

WHY IS GREATER TRANSPARENCY NEEDED?

European Union law lays down the need for transparency and establishes the basic right of access to documents. The European Medicines Agency has implemented policies on the publication of decisions on requests for MAs and of clinical data, improving the information available to patients, carers and healthcare professionals. Greater transparency can also help foster innovation and stimulate research.

These principles should equally be applied to ATMPs approved under HE but this is not always the case across all EU Member States.

The preamble of the ATMP regulation clearly states the need to ensure that Community rules regarding quality and safety should not be undermined. Therefore, it is essential to make available information on the use of HE products across the EU in order to provide information on treatment options for patients. Knowledge of available clinical data generated from use of HE products can inform the safety assessment of similar ATMPs.

A CENTRAL, PUBLICLY AVAILABLE REPOSITORY OF ALL HE PRODUCTS ACROSS ALL EU MEMBER STATES SHOULD BE ESTABLISHED

Access to ATMPs under HE is by the nature of the underlying legislation more restrictive, i.e. limited to the Member State that grants the HE. Limited public knowledge on products available in different Member States makes it impossible for patients to travel to another country for treatment; furthermore, information on the efficacy and safety profile of these products is limited.

EBE and EFPIA recommend the creation of publicly available central repository listing all HE products across Member States, with the name of the manufacturer or licence holder, and their indication of use.

Understanding availability and use of products under HE across all Member States will help inform patients without therapeutic alternatives about innovative treatment options and promote transparency on the quality, safety and efficacy of products being used under HE. Greater transparency of ATMPs under HE will also allow greater scrutiny and assurance that the system is being used as intended.

Increase knowledge on efficacy and adverse reactions for ATMPs available under hospital exemption

EBE and EFPIA consider increased transparency regarding clinical data, including efficacy and adverse events, for ATMPs available under HE essential to accumulate knowledge in this dynamic and rapidly evolving field.

Currently there is limited knowledge on use and availability of ATMPs (individual products and product types) under HE and their quality, safety and efficacy profiles. Quality and safety data are key elements for understanding mechanisms of action (both known and unforeseen). Increased transparency on data from use of HE products can foster current and future development of ATMPs, and could lead to important progress in the field.

As already required by some Member States, annual reporting of data on quality, safety and efficacy of products available under HE to national competent authorities should be mandatory. Furthermore, national competent authorities should provide a public summary of their assessments of these data; this could be achieved via the proposed central repository in the same way that scientific conclusions and assessment reports are made available by the European Medicines Agency for centrally authorised medicinal products.



3. Conclusion and Call to Actions

EBE and EFPIA consider that patient equality in access to innovative medicines and in particular ATMPs needs to be addressed as a high priority by the EU Member States. Therefore, EBE and EFPIA call for transparent implementation and convergence of HE across all EU Member States in a manner that could help foster innovation in the ATMP field. Any approach taken to improve HE use and implementation should align with the aims of the ATMP Regulation to incentivise research and development of innovative ATMPs across all types of ATMP developers and prioritise those ATMPs that can be made accessible across the EU under a centralised marketing authorization.

EBE and EFPIA call on the European Commission to improve patient safety and access to effective therapies in the field of ATMPs through two actions:

1. Development of a 'best practice guide' on national implementation of hospital exemptions for ATMPs. This would help ensure that similar standards for patient safety and product quality and safety are implemented across all EU Member States, ensuring equitable treatment of all patients. It should address at least the following points:
 - Give a European harmonised definition for "prepared on non-routine basis".
 - Define eligibility criteria for products to be approved under HE. "Unmet medical need" should be a key criterion, defined as no approved product available for the same indication and patient group in the Member State.
 - Justify HE approval and subject it to annual renewal (in order to allow identification of new centrally approved products for the same indication and patient group that have become available after an HE has been granted).
 - Support a risk-based approach toward authorisation of manufacture and use of HE products that considers the complexity of the construct and manufacturing process.
 - Steer products used under HE towards clinical trials for marketing authorisation when possible (as HE could impact clinical activities for products under development for the same indication, particularly for rare diseases).
 - Require the hospital, prescriber and manufacturer to collect and submit an annual report on safety and efficacy data to the national competent authority for improved transparency.
2. With the support of national competent authorities, development of a register of all ATMPs made available under HE, that
 - Lists all HE products available across all EU Member States;
 - Shows that the hospital, prescriber and manufacturer have collected and submitted an annual report on safety and efficacy data for the HE product concerned to the national competent authority;
 - Ensures visibility and transparency of the relevant national competent authority's assessment of annual safety and efficacy data for HE products in the form of a public summary of assessment, as is currently expected for clinical trial data and EPARs for centrally authorised ATMPs.

This would improve transparency on HE products for all interested parties, informing:

- **Patients** on potentially available treatment options,
- **Health care providers** on potential treatment options for their patients as well as safety and efficacy on such treatments,
- **National competent authorities** on situations where other treatments exist for indications for which an HE has been requested as well as demonstrating regulatory oversight,
- **Manufacturers and developers of ATMPs** on unmet medical need where fully authorised products are needed as well as relevant clinical experience.

With the above actions we would better protect patients, incentivise development of ATMP products and promote broad patient access to these novel therapies across EU.