

EU ATMP Hospital Exemption

Position paper

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Summary

- The Hospital Exemption has a legitimate role to play in meeting unmet patient needs. Equally, action should be taken to ensure that the use of the exemption does not undermine the rights of patients to safe and effective treatment.
- The Hospital Exemption should be interpreted and implemented in a strict and fully harmonised manner by all EU Member States, recognising that the exemption should only be applied in the absence of centrally authorised medicinal products. Commission guidance should support National Competent Authorities in achieving harmonisation.
- Measures should be adopted to improve transparency of the use of the Hospital Exemption, including though the establishment of a register of exempted products and the adoption of a harmonised Informed Consent Form.
- To safeguard incentives for innovation, steps should be taken to ensure the Hospital Exemption cannot be used an alternative route to market for developers of ATMPs.

The ATMP Regulation and the 'Hospital Exemption'

Article 28 of Regulation 1394/2007/EC (hereafter, the ATMP Regulation) on advanced therapy medicinal products (ATMPs), referred to as the 'Hospital Exemption' (HE), foresees the exclusion of certain ATMPs from the scope of Directive 2001/83/EC on medicinal products for human use. Instead, national procedures regulate the preparation and manufacturing of such medicinal products. These products are defined in the ATMP Regulation as: *"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"*.

The HE allows Member States to permit the manufacture and use of ATMPs in their territories without fulfilling the requirement for submitting a marketing authorisation application to be assessed by the Committee for Advanced Therapies (CAT) and Committee for Medicinal Products for Human Use (CHMP) within the EMA and an authorisation to be granted by the European Commission. Member States must ensure that the manufacture of ATMPs under the HE is authorised by the National Competent Authority and that manufacturing, traceability, pharmacovigilance and specific quality standards are equivalent to those provided for at EU level for ATMPs which are granted a centralised marketing authorisation. The HE products must be produced in GMP-authorized sites.

Ensuring appropriate use of the Hospital Exemption

The ATMP Regulation and the related legislative framework for medicines is designed to facilitate access to ATMPs while ensuring the necessary level of public health protection for patients, as well as fostering and incentivising the research, development, and authorisation of innovative ATMPs. As such, EuropaBio is generally supportive of appropriate use of this exemption in cases of individual patients with unmet clinical needs and where no centrally approved treatment exists.

While the HE has an important and legitimate role to play in this context, EuropaBio believes that action is required to prevent instances of inappropriate use which go beyond the intent of the ATMP Regulation. Actions are required to address three key challenges:

1. The HE has been interpreted and implemented inconsistently across the EU
2. There is a lack of transparency about how the HE is used
3. Excessive and unjustified use of the HE may create a barrier to innovation.

This paper addresses these challenges in turn and provides recommendations for action. EuropaBio believes that the failure to address these challenges could undermine the effectiveness of the regulatory framework set out by the ATMP Regulation, and, ultimately, undermine the rights of patients to safe and effective treatments.

1. The HE has been interpreted and implemented inconsistently across the EU

Every patient must have full confidence that any medicinal product provided to them has been rigorously assessed to ensure that it is safe to use and has been shown to be effective. The ATMP Regulation and the related legislative framework for medicines are designed to facilitate access to advanced therapies while ensuring the necessary level of health protection for patients, as well as fostering and incentivising innovative research and development.

The HE has been interpreted and implemented very differently across the EU, which risks undermining the protections that are in place for patients. To ensure that patients always receive safe and effective treatments, it is necessary to restrictively apply the HE conditions stipulated in the ATMP Regulation to ensure that the HE is not used inappropriately.

EuropaBio calls on the European Commission to:

- **Clarify that the use of the HE should be restricted to the scenarios stipulated in the ATMP Regulation – for individual patients, within one Member State and on a non-routine basis. As regulatory exemptions should be interpreted conservatively by default, the Commission should make clear that any medicinal products approved pursuant to the ATMP Regulation should take precedence. There should be a harmonised strict interpretation and implementation by the EU Member States to recognise that the HE should only be applied in the absence of centrally authorised products.**

The variation in the implementation of the HE threatens to undermine the single market for advanced therapies as well as to create significant uncertainty for companies seeking to develop and obtain marketing authorisation for innovative therapies. For example:

- In Italy, it is explicit (via a 2015 decree¹) that it is not possible for a HE to be granted if a licensed ATMP is already available, whereas in Spain, France and Germany no such clear restriction exists in national regulations.
- In Belgium, regulations require that more than one patient has been first exposed to the ATMP in a setting authorised by the National Competent Authority (i.e. either in a registered clinical trial or a marketing authorisation), which prevents the HE being used to circumvent the requirements of pharmaceutical development.
- In some Member States, 'non-routine' use is defined as a fixed number of patients whereas other states determine this on a case-by-case basis.

EuropaBio calls on the European Commission to:

- **Collaborate with the EMA, Heads of Medicines Agencies and National Competent Authorities, to provide clear harmonised guidance which ensures consistent interpretation and use of the HE across all Member States. This guidance should:**
 - **Provide an unambiguous and standardised definition of "non-routine" use and "within the same Member State".**
 - **Clarify how quality and PCV standards should be met.**
 - **Make clear that Member States should ensure that GMP standards for HE products are equivalent to those for authorised ATMPs.**

2. There is a lack of transparency about how the HE is used

Whereas the safety and efficacy of authorised treatments is demonstrated through data collected in clinical trials, there is no requirement to collect information on HE products being used or collect data on their safety and clinical outcomes. Such information should be systematically collected and made accessible to clinicians and patients.

EuropaBio believes that HE products should be publicly listed in European or national databases, together with their essential elements of composition. Their use should be compliant with existing pharmacovigilance requirements. The vigilance system should be shared between the European Commission and EU Member States, allowing for a "post-administration" long-term follow-up with adequate reporting of information on quality, safety and efficacy, in line with products that receive marketing authorisation.

Furthermore, the potential loss of valuable data from clinical trials, which are essential for continued innovation, should be pre-empted. It is important to raise awareness of

¹ Article 3(1) of Decree of the Italian Ministry of Health of 16 January 2015 provides that ATMPs prepared and intended for use under Hospital Exemption can be used (1) only on individual patient and (2) in the absence of therapeutic alternative and (3) in case of urgency and emergency which threatens the life of the patient or a serious harm to him/her health.

the benefits of clinical data collections under the HE with physicians, hospitals, and academic institutions.

EuropaBio calls on the European Commission to:

- **Work with National Competent Authorities and involve EU-funded programmes to establish a register of exempted medicinal products which monitors how these products are used and provides appropriate information relating to their safety and efficacy. Alternatively, National Competent Authorities should maintain a registry of sites, and require individual sites to contribute to a registry providing appropriate information relating to safety and efficacy. We recommend that there is a provision included within Commission guidance that ensures transparency relating to clinical data.**

It is vital that patients are fully informed about their treatment options. EuropaBio believes that a harmonised Informed Consent Form must be completed prior to treatment for all exempted products. The procedures for ethical approval and patient consent should be brought in line with that of clinical trials.

Promotion of an unlicensed medicine contravenes the EU law (Directive 2001/83/EC), and as such HE should not be actively promoted by treating physicians or by patient groups. It is clear from the ATMP Regulation that HE products should only be used for individual patients and should only be administered to patients of the country in which the HE product is developed to comply with the established standards for liability, safety monitoring and related issues. National Competent Authorities should ensure that these therapies are not promoted to 'general' patient populations nor across borders.

EuropaBio calls on the European Commission to:

- **Work with National Competent Authorities to introduce a harmonised Informed Consent Form that must be completed prior to treatment for all exempted medicinal products.**

3. Excessive and unjustified use of the HE may create a barrier to innovation.

It is necessary to ensure that the HE is not used as an alternative route to market, bypassing the central authorisation process as the European Commission warned in 2014.² Without appropriate safeguards, the marketing of HE products in a single Member State could encourage fragmentation of the single market and jeopardise equal patient access to medicinal products. This scenario would create an unintended barrier to innovation, as developers incurring higher developmental costs associated with a marketing authorisation application would be at a competitive disadvantage. As such, EuropaBio believes that the intent for any ATMP prepared

² European Commission (2014), Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 https://ec.europa.eu/health/sites/health/files/files/advtherapies/2014_atmp/atmp_en.pdf

under HE should always be full regulatory approval as laid down in the ATMP Regulation.

EuropaBio calls on the European Commission to:

- **Work with National Competent Authorities to ensure that the HE is not being used by developers of ATMPs as an alternative to the centralised approval pathway as set out in the ATMP Regulation.**

Conclusion

By putting forward these recommendations, EuropaBio and its members would like to engage the European Commission and all relevant stakeholders in a discussion on the future use of the HE in the context of the new EU Pharmaceutical Strategy and its accompanying actions.

About EuropaBio

EuropaBio, the European Association for Bioindustries, is the recognised voice of the European biotech community championing world-class solutions for society's challenges. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a bio-based and zero-waste economy. EuropaBio represents 81 corporate and associate members and bio regions, and 15 national biotechnology associations in turn representing over 1800 biotech SMEs.

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