Reform of the EU General Pharmaceutical Legislation

Joint Position Paper on the Hospital Exemption Scheme for ATMPs

Introduction

In the context of the revision of the EU General Pharmaceutical Legislation, this paper puts forward joint recommendations from ARM (Alliance for Regenerative Medicine), EFPIA (European Federation of Pharmaceutical Industries and Associations), EuropaBio, EUCOPE (European Confederation of Pharmaceutical Entrepreneurs) and ISCT (International Society for Cell & Gene Therapy), for the reform of the Hospital Exemption (HE) scheme for Advanced Therapy Medicinal Products (ATMPs)[1].

What is the Hospital Exemption Scheme for ATMPs?

The ATMP Regulation (EC) No 1394/2007 established the legislative framework for ATMPs in the EU. The backbone of the regulation is the mandatory requirement for all ATMPs to obtain a centralised marketing authorisation before they can be placed on the market in EU Member States.

Article 28(2) of the ATMP Regulation, as implemented in Article 3(7) of Directive 2001/83, introduces the Hospital Exemption (HE) scheme, which empowers Member States to permit the provision of an advanced therapy, without marketing authorisation, under certain conditions. More specifically, HE products must be prepared on a non-routine basis in accordance with specific quality standards and confined within a single Member State. This must be undertaken in a hospital, under the exclusive professional responsibility of a medical practitioner to comply with a medical prescription for a custom-made product for an individual patient.

As an exemption, the HE should be interpreted strictly and apply only when no authorised medicinal product is available. However, the different interpretations and implementations of the scheme across the EU has led to a situation where the HE is used in a large series of patients in some Member States, including when a fully developed ATMP has been authorised by the EMA for the same indication.

The HE scheme has an important and legitimate role to play in ensuring access to potentially lifesaving treatments for areas of unmet needs. Our position remains that the HE scheme is and should continue to be seen as an important *exemption* within the EU's regulatory framework, allowing for the manufacturing and use, in a clinical setting, of an advanced therapy made in line with Good Manufacturing Practice (GMP)

[1] ATMPs are innovative therapies that encompass gene therapies, somatic cell therapies, and tissue-engineered products. These so-called regenerative medicines can augment, repair, replace and even regenerate organs, tissues, cells, genes, and metabolic processes in the body. These are often referred to as groundbreaking therapies as they have the potential to address the root cause of diseases, and therefore potentially cure them.

standards, for an individual patient with a medical need, subject to specific conditions. In light of the diverse interpretation and use of HE across the EU, clearer rules are needed on when and how the HE can be used to ensure that this exemption is applied consistently by Member States, according to its intended purpose.

Our organisations welcome the European Commission's intention to reduce inconsistencies in the interpretation and implementation of the HE scheme across EU Member States. The objective to improve transparency of HE approvals, with the creation of an EU repository, is warmly welcomed. We believe, however, that changes are needed to the European Commission's proposal (Article 2 and Recital 18 of the proposed Directive) in order to reduce uncertainty on the use of the HE, ensure strong quality and safety standards, and to preserve the integrity of the single market.

More specifically our organisations have the following recommendations concerning Article 2 of the proposed Directive:

- Further clarity should be provided on when the use of HE is appropriate, namely that it is a legitimate exemption when there are no authorised treatments nor clinical trials for which the patient is eligible.
- The Article should specify that the HE approval is for one year and that the granting of a possible extension should be conditional to an assessment of whether the HE is still in the interest of patients, including that no centrally authorised ATMP treatment has been made available since the HE approval was granted nor that there is an adequate clinical trial option.
- A definition of the term 'non-routine use' should be added to ensure that the HE is applied appropriately and in a harmonised manner across the EU.
- The proposed repository and EMA reports on the use of HE should be made publicly available to ensure transparency on the use of HE and provide healthcare professionals with the necessary information to safely treat and follow-up patients. The Directive should also require patient follow-up for a sufficient period of time following the administration of the HE product, so that data on safety and efficacy can be properly captured for the benefit of the concerned individuals as well as patients who may be treated with the product in the future**.**
- The reference, in Recital 18, to the possibility for the Commission to develop an adapted framework for less complex ATMPs should be deleted, as the HE already provides for an adapted framework.

Unintended consequences of the current use of the HE

As with all exemptions from EU legislation, the HE should be interpreted strictly in accordance with the original intention of the provisions, to provide the possibility to receive an advanced therapy in exceptional situations. The HE was designed for limited use and not as an alternative pathway to develop products and conduct clinical trials.

In practice, the interpretation of the HE has varied widely between Member States, resulting in deviations from its intended purpose, including the risk of being used as a parallel track to place ATMPs on the market without a marketing authorisation. A study from ARM[2] highlights how current HE practices could negatively impact the European ecosystem for ATMPs.

[2] A. Hills et al, An assessment of the hospital exemption landscape across European Member States: regulatory frameworks, use and impact, Cytotherapy, December 2020

The main challenges linked to the existing use of the HE include:

- **Limited availability of data**: Due to the framing of the HE provisions in the EU legislation, there is no consistent long-term follow-up data on efficacy and safety of HE products. Some Member States have undertaken the important task of establishing data collection systems. However, the incomplete, inconsistent, and non-harmonised approach to data collection, scientific evaluation, transparency, and communication presents significant challenges for long-term patient follow-up and understanding of the use and impact of HE products. Therefore, we strongly welcome the Commission's proposal to standardise and institutionalise the collection of data regarding the use of HE (proposed Directive Article 2.4 and Article 2.7(b)).

- **Impact on the EU single market and the regulatory system:** The EU legislation lacks a definition of 'non-routine' which creates uncertainty regarding the role of the HE when a centrally authorised product becomes available. This uncertainty makes the EU regulatory framework less attractive than other regions for ATMP development. Furthermore, when the HE is used in a way which is different than what was intended, such as a parallel regulatory track to marketing authorisation, the HE risks to negatively impact the competitiveness of the EU regulatory framework and dilutes the practical effects of the marketing authorisation principle. This results in a distortion and fragmentation of the EU single market which must be avoided, both for patient safety reasons as well as to maintain Europe's attractiveness for companies in the sector, and ultimately, to ensure that patients in Europe will continue to benefit from transformative therapies. Europe is already trailing behind Asia and the US in terms of the number of therapeutic developers, new clinical trials, and investment into the ATMP sector[3]. Developers would be further disincentivised to invest in complex, costly and risky clinical development activities in Europe if they have had to compete with others that do not face the same requirements.

- **Quality, safety, and efficacy:** Due to the structural complexity of ATMPs, where the manufacturing process largely determines the efficacy and safety of the product, tight process control and the highest quality standards must be applied to products. Small changes in manufacturing can cause distortions in the product specification and render a product ineffective or unsafe. This further underlines the importance of GMP standards which HE products must abide to. However, there are differences between Member States regarding how they meet traceability and pharmacovigilance requirements, as well as quality standards that are equivalent to those provided for at EU level, as per Directive 2001/83/EC.

- **R&D on ATMPs:** Although data collected from a HE product has sometimes been used as formal clinical evidence, a potential negative effect of the proliferation of the HE is diverting patients from controlled clinical trials, potentially delaying the collection of evidence-based data for new products and reducing an already limited clinical trial population pool. Patients receiving treatment under the HE may become ineligible for future clinical trials impeding development of future products that can benefit other patients.

Our recommendations

Our organisations welcome the European Commission's intention to address unintended consequences that have resulted from the differences in implementation of the HE among the EU Member States. In

[3] Alliance for Regenerative Medicine sector data

particular, we are encouraged to see that Article 2 of the proposed Directive moves towards greater harmonisation and transparency on the use of the HE across the EU. However, to ensure the appropriate use of HE and mitigate the risks of differences in the implementation of the Directive by Member States, we believe that additional clarity and safeguards are needed in the text. In the interest of patient safety, a well-functioning EU single market, and the competitiveness of the EU in the ATMP sector, we jointly make the following recommendations for the HE provisions in the EU pharmaceutical package:

- **The HE should stay exceptional:** The HE has an important and legitimate role to play for individual patients or small groups of patients where there are no clinical trials nor centrally approved alternatives that can satisfy the specific needs of the patient. The revised legislation should clearly specify that the HE cannot be used when the EMA has authorised an ATMP for a given indication and population group. When assessing an application for an HE product, the National Competent Authorities (NCAs) should verify that there is currently no authorised ATMP for this therapeutic indication. In the situation in which there is an investigational advanced therapy available as part of an ongoing clinical trial, NCAs should only authorise an exemption if the individual patient is not eligible for the programme. Clinical trials should always be preferred to the HE, as their review process offers a higher safety standard to patients, and the insights gained during the study can benefit other patients. We recommend the development of clear EU rules within this regard, including minimum requirements for HE product applications within the revised Directive.

Proposal: Article 2 of the proposed Directive should provide further clarity around the scope of when the use of HE is appropriate, namely that it is a legitimate exemption when there are no authorised treatment for these patients nor clinical trials for which the patient is eligible.

- **Granting of the HE on a time-limited basis:** As an exemption, the HE approval, referred to in Article 2(2) of the proposed Directive, should be granted only for a period of one year[4]. Before granting a possible extension of the HE approval, a review should be undertaken to determine if the criteria are still met. Should hospitals apply for an extension of the HE approval, a report with the minimal safety and efficacy data collected so far and a justification of why the HE is still in the interests of patients should be provided, including that no centrally authorised ATMP treatment has been made available since the HE was granted, nor that there is an adequate clinical trial option.

Proposal: Article 2 of the proposed Directive should specify that the HE approval is for one year and that the granting of a possible extension should be conditional to an assessment of whether the HE is still in the interests of patients, including that no centrally authorised ATMP treatment has been made available since the HE approval was granted nor that there is an adequate clinical trial option.

- **Harmonisation and clear definitions:** Providing clear definitions in the proposed Directive would ensure a consistent interpretation of the HE in all EU Member States. The concept of the use of the HE on a 'non-routine' basis should be clearly defined to ensure that the exemption is applied appropriately. Currently, non-routine is either not defined by law or defined differently (e.g., in some countries it is defined as a preparation for a maximum of a few patients and in others it

[4] There is precedent for the one-year timeframe - e.g. conditional Marketing Authorisations need to be renewed annually.

reflects small-scale use).[5] To meet the definition of non-routine, HE products should be produced exceptionally to respond to the needs of individual patients. Any standardization of the process or claims of industrialised manufacturing should be understood to deviate from the concept of non-routine. Although some autologous therapies may be considered non-routine, an autologous therapy in itself does not automatically mean it is produced on a 'non-routine' basis because they may be subject to complex and scaled manufacturing processes involving specialised facilities and techniques for their collection, isolation, expansion, manipulation, and formulation.

Proposal: Article 2 of the proposed Directive should include a definition of the term 'non-routine use', to ensure that the HE is applied appropriately and in a harmonised manner across the EU.

- **Data repository, transparency, and patient safety:** Our organisations welcome the proposal in Article 2 of the proposed Directive that the EMA shall set up and maintain a repository with data on the use, safety, and efficacy of HE products. Such a repository should be publicly accessible and include a list of products under the HE scheme to ensure transparency on its use across Member States as well as ensure scrutiny and assurance that the system is being used as intended by EU legislation. The repository should also maintain a clear overview in relation to safety (e.g., including adverse events) and collect the same efficacy data as for centrally authorised products, thus contributing to the accumulation of potentially relevant clinical information. Furthermore, a mandatory patient follow-up for a number of years, based on product risk, should be requested for patient safety purposes and to evaluate the efficacy of HE products. To support the evaluation of the use of HE by the EMA, it is also appropriate that decisions of NCAs to approve or refuse HE products should outline the reasons for the decision and be made available in the repository.

Proposal: Article 2 of the proposed Directive should require that the repository and EMA reports on the use of HE be made publicly available to ensure transparency on its use and provide healthcare professionals with the necessary information to safely treat and follow-up on patients. The Directive should also require patient follow-up for a sufficient period of time following the administration of the HE product, so that data on safety and efficacy can be properly captured for the benefit of the concerned individuals as well as for patients who may be treated with the product in the future**.**

- **A single framework for all HE products:** Recital 18 of the proposed Directive refers to the possibility of an adapted framework for less complex ATMPs developed and used under the HE. As an exemption, the HE already provides for an "adapted framework" for the development and use of advanced therapies in an hospital setting. Our organisations are concerned that the creation of such a two-tiered system would generate uncertainty, negatively impact the competitiveness of the EU's robust regulatory framework and dilute the practical effects of the marketing authorisation principle. We are equally concerned about the ambiguity around "less complex ATMPs" and which products would qualify. Rather than creating an additional layer to the existing regulatory framework, we believe that it would be more appropriate to establish support programmes to help academic developers bring therapies through the centralised authorisation procedure, building on the ongoing EMA pilot supporting academic and non-profit

[5] Ivaskiene et al. 2016, Coppens et al. 2020, Hills et al. 2020

developers of ATMPs[6].

Proposal: The reference in Recital 18 of the Directive of the possibility for the Commission to develop an adapted framework for less complex ATMPs should be removed.

Conclusions

ATMPs can offer life-changing therapeutic solutions for devastating conditions, many of which have been underserved thus far. As transformative therapies addressing the root cause of the disease, sometimes with a single administration, ATMPs are fundamentally different from conventional medicine. As sophisticated therapies at the cutting edge of innovation, they require a stringent, single regulatory framework to ensure patient safety and the highest quality of healthcare.

The HE has an important role to enable patients to receive an advanced therapy under controlled conditions in cases where no suitable authorised medicinal product nor investigational product are available for a specific indication[7]. We call for the HE to remain a true exemption driven by medical need and ask policymakers to ensure that appropriate safeguards are put in place so that the HE is used appropriately, according to its intended purpose. This is crucial to ensure that patients are protected as much as possible, and that developers will continue to invest, conduct clinical trials, and seek marketing authorisation in the EU, bringing more transformative ATMPs to patients in Europe.

Our organisations welcome the efforts of all stakeholders that endeavour to become ATMP developers. The EMA is currently conducting a pilot to help academic and non-profit developers navigate the regulatory processes and optimise the development of ATMPs[8]. Through this process, the EMA hopes to better understand what additional support or regulatory tools these developers may need. We support this pilot programme and the EMA's initiative on the translation of basic research into medicines that meet regulatory standards for approval.

Academia plays an important role in the development of ATMPs and helps drive innovation in the field, but it cannot unlock the full potential of ATMPs alone. Partnership initiatives between academia and industry should be strongly encouraged, as a critical pathway to ensure applied research science can be more effectively translated into novel, clinical-stage medicines for patients, while at the same time achieving efficiencies and economies of scale. Such partnerships can contribute to closing the gap between world-class basic research conducted at an academic level and specific therapeutic applications in a win-win fashion. We strongly welcome and encourage continued dialogue on the HE, including the role of all developers, and how to improve access to these therapies.

Our organisations are committed to engage with policymakers and interested stakeholders for an inclusive and solutions-driven approach on the HE in the best interest of patients across the EU.

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[6] EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products | European Medicines Agency (europa.eu)

[7] Cuende N et al, Patient access to and ethical considerations of the application of the European Union hospital exemption rule for advanced therapy medicinal products, Cytotherapy, July 2022

[8] EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products | European Medicines Agency (europa.eu)