EUCOPE

European Confederation of Pharmaceutical Entrepreneurs AISBL

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RECOMMENDATIONS FOR GOOD PRACTICE OF HOSPITAL EXEMPTION CLAUSE IN ADVANCED THERAPY MEDICINAL PRODUCTS

1. INTRODUCTION

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer groundbreaking new opportunities for the treatment of disease and injury[1], bringing with them the promise not only of treatment to manage the symptoms of a diverse group of severe, disabling or life-limiting conditions but also the promise of one-time disease-modifying and potentially curative treatments that can transform and save lives.

The principle of hospital exemption[2] (HE) allows for the use of an ATMP without a marketing authorization under certain circumstances[3]. This only applies in a hospital setting on a non-routine basis for an individual patient and when no centrally authorized treatment or clinical trial is available.

EUCOPE and its member companies developing ATMPs are pleased to propose the following recommendations for the good practice of hospital exemption, for the benefit of science, research, and ultimately, patients in Europe.

2. GENERAL PRINCIPLES

Continued advances in ATMPs for patients depends on academic-industry partnership.

Expanding access to ATMPs for patients in Europe requires collaborative research efforts by academia and industry. These partnerships will drive the development of new therapies, improve product safety and efficacy, and drive evidence generation. The manufacturing, use and potential reimbursement of ATMPs produced via a local application of the hospital exemption rule, without a marketing authorization may be **legitimate in certain situations:**

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[1] https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview, accessed 18 March 2020.
[2] Article 28 (2) of the ATMP Regulation No 1394/2007 of the European Parliament and of the Council of 13 November 2007 modified the Directive 2001/83/EC by adding Article 3(7).
[3] Such products must be produced at the request of a physician and should only be used within the Member State where they are produced.

- For research purposes to help discover the next generation of treatment or new applications;
- In case of high unmet medical need when patients are not eligible for an alternative treatment, including a centrally authorized ATMP or as part of a clinical trial.

Substantial differences in their product characteristics have the potential to drive variation in quality, safety and/or efficacy.

ATMPs are complex medicines. Even slight differences[4] in molecular structures, in the cellular composition of the final products, or in the different manufacturing steps that are necessary to ensure consistent high-quality products, can have a major impact on the clinical profile and clinical performances of ATMPs, specifically:

- Chimeric Antigen Receptor (CAR) T-cell therapies [5] comprised of different targeting, transmembrane, co-stimulatory and T-cell activation domains. Any variation can result in a unique CAR-T profile and performance;
- Nuanced manufacturing processes: optimization of critical manufacturing steps, including cell purification and expansion to the appropriate dose, is essential to ensure consistent production of high-quality products.
- tissue engineering products such as ACI (autologous chondrocytes implantation), which are characterized by a high complexity in technology. Differences in product composition, manufacturing-steps, or quality standards can lead to different levels of clinical evidence for efficacy and safety.

Substantial differences in their product characteristics have the potential to drive variation in quality, safety and/or efficacy.

Centrally authorised and hospital exemption ATMPs should not be considered as similar or equivalent products.

EUCOPE acknowledges that hospital exempted ATMPs can co-exist with commercial ATMPs under specific circumstances. However, hospital exempted ATMPs should remain limited to a "non-routine" use, as stated by the ATMP Regulation n.1394/2007. Indeed, centrally authorised and hospital exempted

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[4] EMA Questions and answers on comparability considerations for advanced therapy medicinal products: *"When critical changes are made in the manufacturing of starting materials for ATMPs having an impact on the manufacturing process or the finished product, a comparability demonstration is required to ensure the consistent quality of the product and to ensure that the change does not have an adverse effect on the safety or efficacy profile of the product"*. 2019, https://www.ema.europa.eu/en/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp, accessed on 28 April 2020.

[5] Chimeric antigen receptor T cells (also known as CAR T cells) are T cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy.

ATMPs have substantial differences in approval processes, the latter not undergoing the same stringent regulatory data requirements and post-marketing obligations.

While treatment decisions should always be based on the specific characteristics and circumstances of the individual patient, national competent authorities should carry out an accurate assessment **of the quality, safety and efficacy of the product** before granting an "exemption". Such considerations **should always prevail regardless of the system of production**.

All ATMP production systems for products approved centrally by the European Medicines Agency should be subject to rigorous GMP manufacturing and testing standards. In terms of process monitoring and documentation requirements, ATMP production systems should be continuously monitored by implementing appropriate in-process and product release specifications and documented by product certifications for each patient.

In terms of clinical data and process validation, EUCOPE considers that it is not in the best interest of patients to substitute a centrally authorised ATMP with a less rigorously tested hospital exempted ATMP that has not gone through a robust quality/safety/efficacy assessment.

Hospital exemption and commercially available, centrally approved ATMPs should not be substituted as they are considered different products produced with different manufacturing processes, potentially different starting materials, and different level of quality.

Patients should always be informed and consent to their treatment

EUCOPE believes patients should always be consented and informed about their treatment. This is of significant importance when the decision is made to treat a patient with a less rigorously tested hospital exemption ATMP instead of an approved available commercial ATMP, given the risk unlicensed products may pose to patient safety. Patients should be informed of the level of quality used to manufacture the product and what tests were conducted on the product and starting materials to ensure safety.

In the interest of patients, there is a need to mitigate the potential of misinterpretation of the legislative boundaries around ATMPs that may allow an unapproved product to be substituted for an approved ATMP or given to patients without a sufficient level of evidence of quality, safety and efficacy and regulatory oversight.

EUCOPE believes many improvements could be made in the implementation of the hospital exemption pathway across Europe, which is the most common alternative pathway under which non-commercial ATMPs are being manufactured and used.

3. EUCOPE RECOMMENDATIONS ON THE USE OF HE FOR ATMPS

Appropriate use

Limit the use of HE to situations when there are no centrally authorized ATMPs available in the Member State for the indication and there are no clinical trials available for the same indication with an ATMP in the Member State.

Long term follow-up

The principles of long-term follow-up should apply to commercial and non-commercial manufacturers, including HE producers.

Transparency

Need for publicly available information about HE product at EU and/or national levels (use and safety/efficacy profile).

Harmonisation

Need for further harmonization of HE requirements/licenses and eligibility criteria across all Member States

A. APPROPRIATE USE

1. HE usage should be limited to **situations of high unmet medical need when patients are not eligible for treatment with a centrally authorized ATMP or as part of an ongoing clinical trial with an ATMP**.

Use of a HE product should be medically justified, and it should be demonstrated that an authorized ATMP or medicinal product or clinical trial with an ATMP for the same indication would not be suitable for the patient. HE products are experimental by nature and their use should not solely be driven by economic or political reasons.

Patients should be fully informed about the status of HE products including available data on safety and efficacy as compared to alternative treatment options before and as part of providing consent. When the use of a HE product is justified, long term safety (at least yearly for 10 years) and efficacy data must be collected.

The promotion of HE ATMPs either for medical or economic reasons, should not be authorized as it contravenes the EU legal framework[6] for pharmaceutical products.

[6]. Article 87 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use stipulates that '*Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law*'.

2. Because not all ATMPs are the same, **the complexity of the molecular structure, the starting materials, as well as the manufacturing and administration processes of the ATMPs must be taken into consideration**.

For ATMPs, hospital exemption shall be considered with extreme caution since those products require more complex manipulation during the procurement, manufacturing, quality control testing and supply processes and small changes in those processes can impact patient safety and efficacy in a significant way. In such cases when guidelines exist for administration and handling, they should be followed for both commercial and hospital exemption ATMPs.

B. LONG-TERM FOLLOW-UP

3. The principles of **long-term follow-up for ATMPs should apply to commercial and non-commercial manufacturers**, including HE producers.

There shall be proportionate requirements for conducting pharmacovigilance obligations including the collection of long-term follow-up data to supplement clinical trials information or initial HE products data. This will provide real-world experience to investigate similar long-term safety and effectiveness outcome measures as required for commercial ATMPs.

4. Providing patients' consent has been given, **data must be captured from both ATMPs with a central EU marketing authorization as well as ATMPs** licensed through hospital exemption or provided via an alternative pathway (e.g. named patient / compassionate use).

However, the data must clearly distinguish where products come from (i.e. commercial or hospital exemption) to ensure that appropriate and thorough safety and efficacy assessments can be carried out and inappropriate effectiveness comparisons are avoided.

When long-term follow-up data are available, the regulatory authorities should encourage sponsors, hospitals or physicians to publish them, along with information on the regulatory framework under which the use of these products was authorized.

C. TRANSPARENCY

5. Need for publicly available information about HE products at EU and/or national levels, including ATMPs provided by state health services and private providers, to increase **transparency on the use and on the safety/efficacy data of ATMPs made available nationally under the hospital exemption pathway**.

Such information shall include all data (quality/safety/efficacy/number of patients treated) and results on the use of HE products having received a HE license by National Competent Authorities (NCAs) similar to the information EMA already publishes for authorized products (e.g. European Public Assessment Report and EMA clinical data portal).

D. HARMONISATION

6. Need for further **harmonization of HE requirements/licenses and eligibility criteria across all member states** to ensure equitable patient access to innovative medicines across Europe and to reinforce the centralized procedure path for ATMPs. This includes:

- Harmonizing the definition of “non-routine basis”;
- Requiring ethics committee approval and patient informed consent including a statement about the lack of alternative treatments;
- Harmonizing the GMP, traceability, pharmacovigilance and long-term follow-up requirements for HE products across Europe as well as minimum standards to qualify for HE;
- Requiring annual reports sent by HE licenses holders to National Competent Authorities about the use and safety/efficacy data of HE products, including long-term follow-up.

7. Encourage the European Commission to publish a **“best practice guide” to reinforce the harmonization of HE requirements** and eligibility criteria across Europe; and to regularly monitor how HE is enforced at the national level and publish an “EU mapping of national regulatory frameworks” to list all requirements country by country, publicly inform about differences between countries and reinforce EU harmonization.