ALLIANCE for Regenerative Medicine

16 February 2017.

Position on Hospital Exemption

The article 28 (2) of the Advanced Therapy Medicinal Products (ATMP) Regulation[1] modified the Directive 2001/83/EC[2] by adding the article 3(7), referred to as the 'hospital exemption' (HE), according to which it is permitted to use an ATMP without a marketing authorization under certain circumstances. This clause applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products must be produced at the request of a physician and should only be used within the Member State where they are produced. In addition, the approach of using the HE to treat patients with an ATMP needs to be authorized by the competent authority of the Member State and in accordance with Reg 1394/2007, should comply with the same general requirements for quality, traceability and pharmacovigilance as for authorized medicinal products.

Hospital exemption has been introduced in the European legislation in order to make products available to individual patients on a non-routine basis and at the request of the treating physician. HE enables patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available.

Whilst this objective is highly valuable, ARM believes that the vastly different interpretations and implementations of Article 3(7) of Directive 2001/83/EC across the European Union warrant priority action in order to avoid for HE to be used as a way to circumvent the applicable legal instruments for the marketing of safe and effective medicinal products in Europe.

Indeed, the different implementations across the European Union have led to a situation where HE is used in large series of patients in some Member States, including when a fully developed ATMP has been authorized at community level for the same indication.

This situation can constitute a disincentive to develop ATMPs to current regulatory and manufacturing standards and thereby may delay patient access to innovative therapies and major advances in regenerative medicine. As an ATMP used within the HE framework can only be used in one Member State, this disincentive has the potential to ultimately limit access to patients across the European Union.

If improperly used, HE has the potential to seriously undermine the provision of safe, high-quality health care to European citizens. Standards for patients need to be equal irrespective of the ATMP originator (industry or hospital), notwithstanding the risk-based approach being applied on a case-by-case basis for these products.

The safeguard of public health has been used as the guiding principle for the proposals developed below. ARM does not believe that ATMP Regulation needs to be reopened to implement these proposals.

<u>HE should be limited to situations of high unmet medical need and no treatment alternatives</u>

By definition, HE is limited to ATMPs prepared on a non-routine basis and used in a hospital under the responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual patient. ARM believes that hospital exemption is justified when there is a clear unmet medical need and no treatment alternatives, i.e. when there exists no treatment

for the same indication approved by regulatory authorities or when there is no possibility of recruiting the patient in an on-going clinical trial (particularly in the case of rare indications).

Patients' needs for effective and safe treatment are best met with a product which has gained a marketing authorization after a thorough regulatory review rather than with a product custom-made for hospital use. As a result, HE should not be allowed when an ATMP has been granted a centralised marketing authorization in the same indication and is available in the Member State.

Recruitment in clinical trials with ATMPs, especially those with a restricted patient pool such as orphan medicinal products, should not be hampered by HE practices. It is in the interest of the healthcare community not to delay the collection of evidence-based data on new products. ARM recommends, wherever possible for patients to be enrolled in a clinical trial with an ATMP under development rather than to be treated with a HE product.

In addition, ARM believes that it would be beneficial for HE to be subject to the approval of an ethical committee review on a case-by-case basis, including the patient consent form and a statement about the lack of alternative treatments including under clinical trial schemes. Member States could consider whether the review and approval by an ethical committee could be requested before authorizing the treatment of a patient within the HE framework. Approval by an ethical committee however, would not lift the professional responsibility and liability of the treating physician.

Need for increased transparency and exchange of information:

HE has the potential to provide early access to patient with high unmet need.
However, there is a lack of transparency on products made available nationally under HE and there is no EU wide requirement for physicians using such products to collect data to establish whether the products are safe and effective (beyond the required pharmacovigilance reporting). A publicly available registry of all sites using ATMP under hospital exemption and their therapeutic indications in all EU Member States would be very helpful to increase transparency for all stakeholders.

ARM welcomes efforts from multiple stakeholders across the EU to harmonize the requirements for the collection of safety and clinical outcome data of patients treated with HE products and to encourage the publication or sharing of these data. This would be invaluable for the healthcare community to understand the benefits and risks of ATMPs and would contribute to ensure that safe and efficacious treatments are delivered to patients.

Furthermore, ARM believes that Member States should require establishments operating with a HE licence to report annually to the MS regulatory authority which products they have made available and how many patients have been treated with each and this information should be made publicly available.

ARM encourages the EU Commission to gather current practices of HE and make this information publicly available so that all stakeholders, patients in particular, are better informed of the potential treatment options.

Regulatory requirements for data collection:

To ensure that patients can have confidence in products made available under HE, there should be a requirement that minimal safety and efficacy data on products made available under HE are collected under a protocol agreed with Competent Authorities (CA) of Member States and reported to the national CA. As part of the agreement to allow non-routine, patient-specific treatment under HE, CA

should review each product annually in the content of emerging treatments available under Clinical Trial Authorisation and Marketing Authorisation and encourage the Health Care Professionals to progress their own treatment under a Clinical Trial Authorisation where appropriate.

If hospitals want to repeatedly or regularly use HE in patients for a same indication, they should be encouraged to initiate and request approval for clinical studies that will help generate robust data for the benefit of the patients and scientific communities. Certification for investigational ATMPs manufactured in hospital or research institutions (i.e. intended for clinical studies) should be made possible.

Need for better education and collaboration:

The generation of data adequate to demonstrate the quality, safety and efficacy of ATMPs should be encouraged to eventually enable a marketing authorisation and market access of innovative treatments in all EU Member States. A series of tutorials could support the education of the medical community and research institutions on requirements for ATMPs, clinical studies and marketing authorisation. Additional incentives to stimulate academic/industry collaborations could also help.

Conclusion:

HE is a useful pathway to enable patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available for an indication with a high unmet medical need. However, it is important to ensure that patients are protected from unnecessary risks and that hospital exemption is not misused to circumvent the applicable legal instruments for the marketing of safe and effective medicinal products in Europe. ARM believes urgent and priority action should be taken to this end and formulates the following series of proposals:

Proposals:

- The European Commission should consider issuing guidelines defining more specifically the scope and requirements for HE for ATMPs, stating clearly that when patients have access to an ATMP with a Marketing Authorization, Member States should not authorize HE for the same medical indication. The guidelines should also address the possible interference of HE with recruitment of patients in clinical trials for the same indication.
- In order to increase transparency and exchange of information, it is proposed to have a publicly available registry of all sites using ATMP under hospital exemption and their therapeutic indications in all EU Member States.
- The Member States could consider making HE subject to the approval of an ethical committee review on a case-by-case basis. The submission to the ethics committee would include the patient consent form and a statement about the lack of alternative treatments.
- Initiatives such as tutorials to educate the medical community and research institutions on requirements for ATMPs, clinical studies and marketing authorization could be supported by the European Commission and/or EMA.
- Additional incentives to stimulate academic/industry collaborations could be envisaged at the EU and/or Member States level.

About the Alliance for Regenerative Medicine:

The Alliance for Regenerative Medicine (ARM) is a global, multi-stakeholder organization that promotes innovation, growth, and delivery of transformative treatments or cures for patients suffering from chronic, debilitating, and often life-threatening diseases, many of which are rare diseases. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 250+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patient advocacy organizations, and other members of the global advanced therapies community. The organization's aim is to connect all parts of the innovation lifecycle to address current unmet medical needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org.

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[1] Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products

[2] 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.