Alliance for Regenerative Medicine

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Recommendations for the use of Hospital Exemption

Executive Summary

Hospital Exemption (HE) is a useful pathway to enable patients to receive an Advanced Therapy Medicinal Product (ATMPs) under controlled conditions in cases where no authorised medicinal product is available for an indication with a high unmet medical need. ATMPs aim to address devastating conditions, with high unmet medical need. With rapidly evolving science and technology development, HE should be used appropriately to ensure that patients are protected from unnecessary risks and research in this field is encouraged. It is important to ensure that HE is not misused to circumvent the marketing authorisation and clinical trials procedures in Europe. ARM recommendations for the use of HE have been updated in light of recent findings showing key differences of interpretations and divergences across countries with gaps in legislation and control of HE at national level.

Proposals:

- HE should be limited to situations of high unmet medical need and no treatment alternatives. Whenever possible, priority should be given to the use of products with a marketing authorisation or investigational products used in clinical trials.
- HE should be subject to regulatory oversight requiring the evaluation of minimum quality, preclinical, possibly clinical, data before authorisation could be granted. A EU regulatory guideline setting these minimum standards should be adopted and implemented in a harmonised way across all Member States.
- HE-authorisation should be granted for specific indications, should be limited in time, limited to non-routine manufacturing (i.e. small and limited number of batches) and subject to the collection of minimal efficacy data under a protocol agreed with the competent authorities.
- Pharmacovigilance requirements and reporting of adverse events should be implemented and controlled as per the applicable EU legislation.
- A mandatory registry should be established with publicly accessible information relating to ATMPs produced under HE, including their place of manufacture and use, source of funding, responsible physician, products details with their intended indication, number of patients treated and any safety and efficacy data generated from the HE use.
- HE-products should be manufactured according the GMP Guide for ATMPs, with consistent implementation and control by pharmaceutical inspectorates across Europe.
- In addition to the approval by the National Competent Authorities (NCAs), Member States should consider to also subject HE to the approval by an ethical committee for the ethical components of the HE application before HE can be authorised to ensure patients' informed consent to treatment and to control the lack of better alternative for the patients. Financial or other incentives should be made transparent and the decision for treatment should be guided by patients' safety and interests.
- Academics and hospitals should be better educated about the regulatory requirements for ATMPs and be further encouraged to engage in translational research. Appropriate collaboration with industry should also be considered.

Background

Advanced Therapy Medicinal Products (ATMPs) including cell therapies, gene therapies and tissue engineered products, constitute a new, transformative category of products whose full potential is beginning to emerge. The advanced therapies sector is creating transformative, durable treatments and potential cures for some of humankind's most devastating diseases – many currently untreatable via conventional treatments – through the use of ground-breaking scientific discoveries and technologies.

With the adoption of EU Regulation (EC) 1394/2007 in 2007[1], the European Commission paved the way to set standards for the review and marketing authorisations of Advanced Therapy Medicinal Products (ATMPs). These regulatory standards require product developers to satisfy a number of criteria before they may bring an ATMP on the market. These include: regulatory oversight of pre-clinical and clinical evaluation on the investigational product, adherence to pre- and post-market approval requirements, and demonstration that the product is being manufactured according to current ATMP good manufacturing practices (cGMP) to assure safety, purity and potency of a product before it reaches a patient.

The article 28 (2) of the Advanced Therapy Medicinal Products (ATMP) Regulation modified the Directive 2001/83/EC[2] by adding the article 3(7), referred to as the 'hospital exemption' (HE), and empowers EU Member States to permit the provision of 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.

HE 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, and as an exemption should be interpreted as applying where no authorised medicinal product is available. However 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 authorised at community level for the same indication.

In February 2017, the Alliance for Regenerative Medicine (ARM) published a series of recommendations for the implementation of HE and called for priority action to ensure that it is not misused to circumvent the applicable legal instruments for the assessment of safety and efficacy for authorised medicinal products in Europe[3].

Despite the publication of this and other position papers on the same topic by other, industrial or academic organisations[4,5,6] and the initiation of a reflection process on HE by the European Commission with the Member States as part of the ATMP action plan launched in October 2017[7], no progress has been achieved to date.

In April 2020, the EMA issued a new warning against the use of unproven cell therapies, highlighting that patients using unproven or unregulated cell-based therapies have reportedly suffered serious, sometimes fatal, side effects including infections, unwanted immune reactions, tumour formations, loss of vision and bleeding the brain[8]. In this statement, the EMA re-affirms the importance of the

marketing authorisation and clinical trials procedures to understand and document the effects of cell-based therapies and thereby ensure that future patients are not deprived of access to potentially curative treatments.

In May 2020, the European Academies' Science Advisory Council, together with the Federation of European Academies of Medicine also recently published a report confirming the need for robust, transparent, evidence-based and harmonised procedures for ATMPs and recommending increased transparency and harmonisation in HE procedures[9].

ARM also recently completed a study to analyse how HE has been implemented legally and is actually used in 7 European countries. Results showed great variations in the implementation of HE across Europe, depending on their respective national legal implementation, policy makers' interpretation of HE, the clarity of guidance at national level, reimbursement opportunities and the level of ATMP research and development activities carried out by academic and commercial organisations[10]. This analysis highlighted key differences of interpretations and divergences across countries, with gaps in legislation and control of HE in these countries.

The recommendations below build on the findings of this latest analysis, stressing the need for priority action to ensure common interpretation of HE and address specific concerns, including lack of transparency. As with our previously published position paper, the safeguard of public health has been used as the guiding principle for the proposals developed below.

HE should be limited to situations of high unmet medical need and no treatment alternatives

There are differences in views regarding the potential reasons for using HE, including as a means to bridge treatment of patients between clinical development, to treat patients not eligible for a clinical study, in early stages of development while development of product and manufacturing is still rapidly evolving, or as a way to allow access to ATMPs which show no or low commercial value and will never progress to a marketing authorisation.

Clearly, the HE pathway provides an invaluable opportunity to treat patients with an unlicensed ATMP where no alternative is available. However, in the interest of public health, there must be a clear and common approach to its use. If HE is used in situations where patients could be treated with approved ATMPs, it creates a two-tiered system with different regulatory standards, potentially impacting patient treatment and potentially delaying patient access to innovative therapies and major advances in the field. It has been noted by the EMA that the number of applications for approval of ATMPs has been very limited, in part attributable to factors such as use of products already available at the national level through hospital exemption route[11]. As an ATMP used within the HE framework can only be used in one Member State, the lack of incentive to develop ATMPs to the full current regulatory standards leading to marketing authorisation 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 high-quality health care to European citizens. The gaps in evidence requirements for granting of a HE licence open the possibility that patients are exposed to products where the quality and safety has not been fully assessed. 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.

In addition, there is still lack of understanding on how the terms "ATMPs prepared on a non-routine

basis" have been interpreted by each EU Member state and on how they have been implemented into the national laws. This is perhaps linked to the differences in views on the purpose or acceptable reasons for using HE. As a result, the majority of the countries do not offer any legal restrictions on the number of HE permitted for the same patient/approved under the same HE licence, other instead provide variable numerical limits without any rationale for the mandated cut-off.

To meet the definition of non-routine manufacturing, the manufacturing operations should be irregular, limited, using non-standardised and non-validated processes, with limited industrialisation of the operations. Small changes in the manufacturing process of a cell- or gene-based product can have a profound impact on the quality, efficacy and safety profile of the final product. This is why extensive product characterisation, process validation, with qualification of the premises, equipment, etc. are required to ensure a consistent product quality, efficacy and safety. The level of requirements for a product with a marketing authorisation is clearly different from that of a product made for non-routine use. The batch size is not sufficient as a criterion to determine whether a manufacturing is routine or not. The fact that an ATMP is autologous, i.e. manufactured by using some tissues or cells from the patient as starting material for the manufacture of the ATMP, is not sufficient to meet the definition of non-routine. To date, most of the ATMPs with marketing authorisation approval are autologous; their manufacturing process have been thoroughly characterised and validated and cannot be considered non-routine, despite the fact that one batch is manufactured for every patient to be treated and that the number of patients to be treated can be very limited in rare or ultra-rare conditions.

Based on these considerations, ARM recommends the use of HE in the following situations:

- By definition, ATMPs prepared on a non-routine basis are unlicensed medicinal products and should not be used where there is a registered medicinal product for the same indication that could be used to meet the patient's special need. Patients' needs for treatments for which the safety and efficacy has been fully assessed are best met with a product which has gained a marketing authorization after a thorough regulatory review rather than with a product custom-made and a less established safety/efficacy profile.
- 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 as it is in the interest of the healthcare community not to delay the collection of evidence-based data on new products. As stated in CAT recent statement, '*Circumventing the marketing and clinical trial authorisation procedure makes it difficult to understand and document the effects of cell-based therapies, thereby depriving future patients of access to potentially curative treatments'*. This is particularly relevant for trials with a restricted patient pool such as orphan medicinal products where the recruitment in the trials should not hampered by the HE use.
- ARM believes that hospital exemption is an option of last resort and justified only when there is a clear unmet medical need and none of the above options will suffice. In such case, an experimental, unlicensed product like the ATMPs prepared on a non-routine basis may be used. This product has to be administered 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.

  If the number of patients to be treated with HE becomes significant over time, the initiation of a properly conducted clinical study should be encouraged, so that the safety and the efficacy profile of the experimental treatment could be better characterized and documented. Such data could be then helpful in determining whether the product would warrant further development.

Regulatory oversight and pharmacovigilance requirements:

HE is subject to approval by regulatory authorities in all Member States; however, the data required to gain a HE and the review process vary widely across Europe. For example, some Member States require that some clinical data are available with the experimental product before granting a HE licence whilst it is not required in others. In some countries, a HE licence can be granted in the absence of any preclinical or clinical data, including details on the likely mechanism of actions to justify the intended therapeutic use of the product. Such a gap opens the possibility for using products under HE in unsubstantiated claims, a highly unethical practice that would put patients at risk.

ARM therefore recommends that an EU regulatory guideline setting minimum quality, preclinical, possibly clinical, standards be adopted and implemented in a harmonised way across all Member States for the application and authorisation of HE. This guideline should require that the scientific rationale, with an analysis of the anticipated benefits and risks in the intended indication should be provided by the applicant and the authorisation should be granted specifically for this intended indication.

Further, to ensure that patients can have confidence in products made available under HE, there should be a requirement that, beyond the required pharmacovigilance data, minimal efficacy data are collected after administration of HE-products under a protocol agreed with the National Competent Authorities (NCA) and reported to the NCA.

As part of the agreement to allow non-routine, patient-specific treatment under HE, NCA should review each product annually in the content of emerging treatments available under Clinical Trial Authorisation and Marketing Authorisation to check the lack of better alternative treatments, and encourage the Health Care Professionals to progress their own treatment under a Clinical Trial Authorisation where appropriate. This requires that the HE authorisation is limited in time, such as one year maximum, and that before granting an extension of the authorisation, a verification should be made to check whether it is still justified. This requires hospitals to apply for extension of the HE licence, with a report of the minimal safety and efficacy data collected so far and a justification why HE is still in the interests of patients.

Whilst the EU legislation requires that national traceability and pharmacovigilance requirements for HE products are equivalent to those provided for at Community level in respect of ATMPs for which authorisation is required pursuant to Regulation (EC) n° 726/2004, there remains a lack of harmonisation across Member States' legal frameworks. The nature of adverse events to be reported, the timeframe for their reporting and the appointment of a responsible person vary from country to country.

ARM recommends the implementation of pharmacovigilance requirements as set out in Directive 2001/83/EC[12] (authorized medicinal products), including appointing a Responsible Person to report serious adverse events (SAEs) within defined time limits, i.e. the notification of SAEs as soon as possible but within 7 days for fatal and life-threatening SAEs and 15 days for all other serious AEs. Such requirements should be implemented uniformly across all Member States. Pharmacovigilance data gathered during the period of HE validity, similar to the Periodic Safety Update Report for authorised products (PSUR) and to the Development Safety Update Report for products still in clinical development (DSUR), should be part of the data required to obtain any extension of the HE licence.

ARM also recommends that the follow-up of patients treated with HE-products be determined on the

basis of the risks identified (e.g. oncogenic risk) and a scientific rational. The proposed follow-up period should be part of the protocol agreed upon with Ethical Committee (CE) and Competent Authorities (CA) at the time of the HE licence.

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 concerning lack of transparency in relation to products made available nationally under HE. The collection of data on the safety and efficacy of treatments is of critical importance when it comes to ensuring that patients benefit from the necessary level of protection. While this data is collected and made available as part of clinical trials and for licensed products, information about which exempted products are being used, and their safety and efficacy, is not systematically collected or made publicly available. There is no EU-wide requirement for physicians to collect such data, beyond the required pharmacovigilance reporting. The publication of such minimal data would pursue similar objectives as the EMA's clinical data publication policy (Policy 0070): enhancing public trust and confidence in health authorities' decision, avoiding duplicative work, encouraging innovation and development of new medicines, enabling independent secondary analysis of the data.

To ensure that patients always receive the highest standards of care available, a mandatory registry should be established by each national competent authority, ideally all referenced with links to the national registries on a webpage of the European Commission, to make publicly accessible the following information relating to ATMPs produced under HE:

- Details of the hospital, academic centre(s) and/or commercial manufacturer involved in production, and the source of funding, including the name of the physician responsible for the treatment
- Details of the product and its intended indication
- Minimal data generated from HE use relating to the safety and efficacy of the product (as agreed under the protocol to be agreed with the NCA – see above)
- The number of patients treated under HE.

ARM encourages NCAs to work in partnership with the European Commission to harmonize data requirements and to coordinate the collection and publication of information which can be used to inform patients and the healthcare community about products produced under the HE. This greater level of transparency will be invaluable in ensuring that the benefits and risks of ATMPs are fully understood, thereby helping to ensure that patients with high unmet need receive safe and efficacious treatments.

Manufacturing Standards:

Due to the structural complexity of ATMP's, even small changes in manufacturing process can cause a variance in clinical profile, and therefore cause the concerns in terms of quality, safety and efficacy of the ATMP. The manufacturing process and production systems are therefore critical to ensure patient safety.

The ATMP Regulation stipulates that ATMPs licenced under HE must be manufactured to "*specific quality standards*" which are "*equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required*".

The analysis of HE implementation in 7 Member States showed that all manufacturers for HE products

are required to hold a GMP licence. However, it also showed considerable variability in the language used to describe the manufacturing standards for HE-ATMPs. As the GMP Guideline for ATMPs adopts a risk-based approach, the standards to be applied and the robustness of the manufacturing process for a non-routine HE-product may not be the same as for a fully developed product with a marketing authorisation where full process validation is required.

In order to ensure consistency across Europe, ARM recommends that the same approach be used by pharmaceutical inspectorates to control GMP facilities for ATMP manufacturers, using the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products as published by the European Commission. An alignment of practices across Member States for HE-products could be fostered through the GMP Inspectors Working Group.

Ethical considerations

As for any experimental treatment, it is important that patients are adequately informed about the nature, the anticipated benefits and risks of their treatment so that they can provide their informed consent before treatment with HE-product. ARM therefore recommends that Member States consider the review and approval by an ethical committee to be requested before authorizing the treatment of a patient within the HE framework by the NCA. The ethical committee could assess the unmet medical need, the lack of alternative treatment and could review whether the information provided to the patient is adequate, objective and complete.

Finally, any decision to treat patients with products under HE should be guided by patient safety and interest. Patients should not be charged for their treatment with a HE product. Financial or other incentives for the hospitals or the responsible physician should be as transparent as possible and should not be the key driver to decide on the treatment.

Similarly, the financial impact on the patient should be taken into account and the decision for treatment should be taken in his/her best interest. The ethical committee should play a role to ensure transparency on potential financial incentives and ensure that patients' safety and interest are preserved and guide the treatment choice.

Need for better education and collaboration:

The European Medicines Agency (EMA) has taken several initiatives to raise awareness of physicians and academics on the requirements for ATMPs such as through participation to meetings with scientific and professional organisations or publications in scientific journals.

Recently, the EMA decided to include academia in the list of organisations eligible for free protocol assistance and waive all fees for scientific advice for academia developing orphan medicines. This was made to further encourage the development of treatments for rare diseases by helping the academia and innovators to navigate the regulatory process and ultimately to translate their discoveries into authorised, patient-focused medicines.

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. As hospitals and academics are not sufficiently resourced and do not typically have the expertise to conduct full product development leading to EU marketing authorisation, translational research and industry-academic collaboration should be further encouraged.

ARM believes that the educational efforts undertaken by the EMA should be further pursued at national level by the national regulatory agencies to raise awareness of academics and hospitals on the regulatory requirements for ATMPs. This would also require that regulatory authorities take a more proactive role to control suspected cases of unregulated use of ATMPs, including stem cell clinics.

Conclusion:

ATMPs aim to address devastating conditions with high unmet medical needs. Gaps in regulatory oversight for the use of unapproved therapies under HE may be detrimental to patients and undermine public trust in science. The above recommendations aim to ensure that HE is interpreted and implemented in a harmonised way across Europe and is used in a responsible, science-based, way to protect patients' safety and interests. ARM strongly encourages the European Commission to address the issues highlighted above as part of its pharmaceutical strategy for Europe and for Member States to implement the above recommendations at national level.

ARM is committed to engage and bring the ATMP sector's perspective in an inclusive and solution-driven dialogue with the Commission, Member States and all interested stakeholders to facilitate the development and access to innovative treatments for the benefit of patients.

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About the Alliance for Regenerative Medicine:

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organisation dedicated to realizing the promise of advanced therapy medicinal products (ATMPs). ARM promotes legislative, regulatory and reimbursement initiatives in Europe and internationally to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing ATMPs. In its 11-year history, ARM has become the voice of the sector, representing the interests of 350+ members worldwide and 70+ members across 15 European countries, including small and large companies, academic research institutions, major medical centres and patient groups. To learn more about ARM or to become a member, visit http://www.alliancerm.org. Transparency register number ID: 244710319190-73

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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.

[3] Alliance for Regenerative Medicine – Position paper on hospital exemption, 16 February 2017. Available at https://alliancerm.org/wp-content/uploads/2018/03/ARM_position_on_HE_final.pdf

[4] EFPIA & EBE - Hospital Exemption for Advanced Therapy Medicinal Products (ATMPs): greater transparency needed in order to improve patient safety and access to ATMPs, 10 October 2017, available at https://www.ebe-biopharma.eu/wp-content/uploads/2017/10/EBE-EFPIA-Position-Paper-on-HE-Final-10.10.2017.pdf

[5] League of European Research Universities (LERU), Advanced Therapy Medicinal Products, Briefing paper No. 3

- September 2019, available at https://www.leru.org/publications/advanced-therapy-medicinal-products

[6] Eucope, Recommendations for Good Practice of Hospital Exemption clause in advanced therapy medicinal products, 29 April 2020, available at https://www.eucope.org/wp-content/uploads/2020/05/eucope_hospital_exemption_recommendations_april2020.pdf

[7] European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs, Launched in October 2017, last updated on 17 Feb 2020, available at https://www.ema.europa.eu/documents/other/european-commission-dg-health-food-safety-european-medicines-agency-action-plan-advanced-therapy_en.pdf

[8] EMA/CAT/94295/2020 Committee for Advanced Therapies 'EMA warns against using unproven cell therapies – 28 April 2020.

[9] EASAC policy report 40 - Challenges and potential in regenerative medicine, May 2020, available at https://easac.eu/fileadmin/PDF_s/reports_statements/Regenerative_Medicine/EASAC_Regenerative_Medicine_Web-ready_complete_1_June_2020.pdf

[10] A. Hills et al. An Assessment of the hospital exemption landscape across European Member Sates: Regulatory frameworks, use and impact. Submitted to Cytotherapy.

[11] EMA Regulatory Science Strategy to 2025, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

[12] Article 107(3) and 107a(4) of Directive 2001/83/EC