SPANISH ADVANCED THERAPY NETWORK "TERAV" POSITION ON THE REVISION OF THE REGULATION OF THE "HOSPITAL EXEMPTION"

20 October 2023

The Hospital Exemption rule is a valuable European legislative scheme that results in a benefit for patients, as it facilitates access to new advanced therapy medicinal products (ATMPs) approved under rigorous control by the competent authorities of the Member States of the EU.

The current proposed revision of the legal framework represents a unique opportunity to harmonize the current framework among the Member States, establishing measures for the collection, and reporting of data as well as periodic review of these data by the competent authorities, and ensure full transparency regarding hospital exemptions decisions. The aim of this revision should be the benefit of the patients, improving their access to new therapies[1]. With this view, we support the text in the proposal released by the EU Commission on the 26th of April 2023[2].

The ENVI Committee of the EU Parliament released on the 3rd of October of 2023 a Draft report proposing amendments to the proposal for the Directive, that substantially modify the hospital exemption regulation and that we believe will jeopardise the access of patients to advanced therapies and the development of science and new advanced therapies in the EU. The proposed amendments are not aimed to improve the safety or accessibility for patients to ATMPs, but rather to benefit the commercial interest of the industry without having any impact on safety or accessibility for patients. Furthermore, it will have a significant negative impact on the scientific development of academic institutions.

The main issues are:

Amendment 30
Article 2 – paragraph 1 a (new)

[1] Role of Hospital Exemption in Europe: position paper from the Spanish Advanced Therapy Network (TERAV). Bone Marrow Transplantation; https://doi.org/10.1038/s41409- 023-01962-0

[2] 2023/0132 (COD). Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

This amendment relates to the suggestion from the Pharmaceutical Industry[3] to strictly define what is considered "*non-routine*", with the aim to oblige any product that could be of interest to the pharmaceutical industry to go exclusively through the industrial manufacturing and marketing authorization pathway, to prevent any possible coexistence and competition between industrial marketed products and academic or non-profit products authorized under the hospital exemption. To that end, the amendment proposes two restrictions:

I) Proposal to limit Hospital Exemption approvals using a restricted concept for a "non-routine" preparation

As it has been suggested by the EFPIA, the ENVI Committee proposes to restrict the hospital exemption to "non-routine" preparation and define this as a product prepared "***on an incidental and exceptional basis to meet the special needs of an individual patient, where there is neither a centrally authorized medicinal product available, nor an ongoing relevant clinical trial or compassionate use programme for the same indication with an advanced therapy medicinal product for which the patient is eligible in the Union".***

These limitations would be deeply damaging to advanced therapies development and to patients' access to advanced therapies, especially for those patients with rare diseases and higher unmet medical needs. These restrictions mean, among other negative consequences that:

- New approvals to academic products under HE would be forbidden if there is ANY centrally authorized product for the same indication, no matter how different the academic product is, or if it is preferable for different profiles of patients or if it appears more effective or safer. Not all ATMP products are commercially attractive for the industry, and this is not a reason to forbid them, particularly considering that HE approval means that those products fulfil requirements of quality, efficacy and safety that are considered, by the national competent authorities, equivalent to the requirements of the centrally authorized products.
- The fact that a specific ATMP product is centrally authorized does not mean it is available (effectively marketed and reimbursed) in all Member States. Sometimes, the reason is a lack of agreement between the MAH and the Member State's competent authority, sometimes it is an unfavorable health technology assessment, and sometimes it is the MAH's own decision not to market the product in a specific country/ies. There are many examples of centrally approved

[3] EFPIA. Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. October 2023. https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf

ATMPs that are not available in some or even most/all Member States (e.g. Zynteglo, Abecma, etc.).

- New approvals to academic products under HE would be forbidden if there is ANY product undergoing clinical trials or compassionate programs for a similar indication. In addition to the concern expressed above, this is even more difficult to accept, because not all medicinal products under development will be finally approved and, if so, the "therapeutic indication" will be decided at the time of approval, after careful benefit-risk assessment of the results obtained in clinical trials. The final indication of the product might well be much more restricted than the indication initially pursued. So, it is unacceptable to prevent the patients' treatment with a product assessed and approved by the competent authorities (HE) just because there is another potential product in development. It should be remembered that many centrally approved ATMPs come from agreements between industries and academia to bring an academic product to a marketing authorization; and approvals to academic products under HE are sometimes a bridge towards a marketing authorization. Limiting HE and only support those developments that, from the very beginning, appear profitable for Companies with a view of centralized industrial manufacturing and a global supply for the whole EU, would be deeply negative to the progress in the field and harm the interests of patients whose treatments are less profitable
- The fact that there is "*an ongoing relevant clinical trial or compassionate use program for the same indication with an advanced therapy medicinal product for which the patient is eligible in the Union*" does not mean that a specific patient can be readily included in that clinical trial regardless of the clinical sites and countries participating in the clinical trial and other organizational aspects of the study.
- A compassionate program with an investigational product (of uncertain safety and efficacy, not assessed by the competent authorities) cannot be preferable to the patient inclusion in a HE program, which has been properly assessed and approved by the National Competent Authorities.

We consider that there is no option to refine and reword those limitations to get an acceptable framework that protects science and patients' access to different products at the time it ensures the financial return of companies' investments in industrially manufactured products. The establishment of a regulatory procedure to decide, case by case, if a HE deserves approval (i.e. it has a different mechanism of action, targets a different population, is somewhat better,..) would be an unbearable burden to the agencies and the academia, with similar negative consequences.

In addition, the very concept of the HE in the directive, defined as an exemption to the main rule, which is the marketing approval foreseen in article 1, implies that the competent authorities should find justified to grant an exemption approval, meaning that there should be an expected benefit for the patients from the HE approval.

Finally, those limitations are against amendment 188 already approved by the EU Parliament to the Article 62 – paragraph 3 of the proposal for a regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin (SoHo) intended for human application. The amendment states that "In cases where the availability of SoHOs or products derived from them depends on potential commercial interests, each Member State shall ensure that those SoHO entities, within the limit of their responsibilities, provide an appropriate and continuous supply of SoHOs, or their derivatives, to patients in their territory. Member States shall negotiate fair and transparent prices for SoHO-derived products that are based on altruistic and unpaid donations. Member States shall also ensure that affordable products are available to patients and that there is continuous investment in research and innovation in relation to those products."

As a conclusion, in our opinion, the amendment suggested by the EFPIA and the ENVI Committee should be deleted, and the original text of the Commission should be maintained.

II) Proposal to limit Hospital Exemption approvals through the definition of procedures of a "non-routine" preparation

The final part of the amendment 30 proposed by the ENVI Committee states that:

"The following measures shall be an indication that an activity occurs on a routine basis:
(a) the manufacturing of a product using standardised or repetitive processes.
or
(b) the use of processes that involve planning in advance, beyond what is needed to address the immediate clinical needs of individual patients".

Manufacturing of ATMP should follow Good Manufacturing Practices (GMP) in all cases, also in manufacturing HE products and even investigational ATMP for clinical trials.
The proposed examples are not relevant because GMP compliance always entails the use of processes as standardized as possible. This would also contradict the amendment for article 2, paragraph 2, subparagraph 2: "The application shall include evidence on quality, safety and efficacy of the advanced therapy medicinal products prepared under hospital exemption." In our opinion it is impossible to submit quality, safety and efficacy data for a product that is not manufactured using a standardized/repetitive process.
Also, the planning in advance and the preparation of several clinical doses or frozen intermediate products could be a useful tool to lower production costs and to make the most of any altruistic donation, as well as a tool to have an allogeneic product ready to be used when a patient needs it.

Therefore, we also propose to completely delete this paragraph.

Amendment 31:
The hospital exemption approval shall be valid for a period of 12 months

This new limitation has not been properly substantiated, and it goes against most of the current national regulations, which normally establish authorizations for a period of 3 to 5 years[4]. This also poses an unnecessary additional burden to National Competent Authorities and academia. We strongly recommend deleting this new restriction and leaving this decision to Member States, which may tailor the conditional approval and its duration on an individual basis.

In conclusion,

- It does not seem justifiable that the hospital exemption pathway should be limited in such a way by interests of an industrial nature. The limitations should not be different from those applicable to ATMPs of industrial origin, both in terms of co-existence with other advanced therapies (i.e. therapeutic indication) and in the duration of the approval.
- The limitations proposed by such an amendment assume that hospital exemption-approved ATMPs might not reach the same level of rigor as that applied to centrally approved ATMPs. These limitations are entirely unnecessary because Medicines Agencies cannot approve a product that, in all aspects and for all patients, is inferior to an already marketed and available product or does not meet the standard regulatory requirements.
- Competent authorities remain the responsible bodies to ensure that the regulatory requirements to grant a HE are fulfilled and the establishment of a central public registry, which is welcomed, will transparent this regulatory guarantee.
- The aim should be to ensure that altruistic and unpaid donations of cells and tissues will give access to affordable advanced therapy products that completely fulfil the quality, efficacy, and safety requirements of the regulatory agencies, as well as fostering research and innovation to obtain new products that address the medical unmet needs of the patients, also when the products are not commercially attractive for industries.

And therefore, we respectfully request to completely withdraw the amendments 30 and 31 proposed by the ENVI Committee.

[4] https://www.bag.admin.ch/dam/bag/de/dokumente/biomed/transplantationsmedizin/studie-hospital-exemptions-atmp-eu-2022.pdf.download.pdf/studie-hospital-exemptions-atmp-eu-2022.pdf.