ALLIANCE for Advanced Therapies

National Implementations

Focus Hospital Exemption on Developing Innovative and Safe Treatments for Patients

Summary

The Alliance for Advanced Therapies (AAT) appreciates and supports the Hospital Exemption as a means to offer individual patients a treatment with a customized, innovative and safe product, particularly when a disease occurs so rarely that the regular development and validation of the required therapy is not feasible. However, AAT would like to emphasize that the inconsistent implementation of the Hospital Exemption in the Member States and routine preparations of treatments under an exemption impede the development of new safe and effective treatments. Therefore, the Alliance believes that a harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients. It is in the best interest of patients to limit Hospital Exemptions to non-routine preparations of treatments based on article 28 of European Regulation 1394/2007 under all applicable safety and quality rules. Furthermore, Hospital Exemptions should no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal Product (ATMP) is available. At this moment, there is no European-wide legal certainty on this point.

The Basis: European Regulation on ATMPs

The Hospital Exemption (HE) is outlined in article 28 of the European Regulation 1394/2007, published in November 2007. This article provides for the implementation of national procedures and control measures to regulate the manufacturing and use of certain non-routinely produced ATMPs outside the scope of the ATMP directive."

Article 28 specifies that an ATMP only qualifies for a Hospital Exemption if ***all*** of the following criteria are met:

- Preparation on a non-routine basis
- Preparation according to specific quality standards (equivalent to those for ATMPs with a centralized marketing authorization)
- Use within the same Member State
- Use in a hospital
- Use under the exclusive responsibility of a medical practitioner
- Comply with an individual medical prescription for a custom-made product for an individual patient.

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With these criteria, the European legislators intend to provide patients with the possibility to benefit from a custom-made, innovative, individual treatment in the absence of valid therapeutic alternatives, under the strict condition that Community rules related to quality and safety are not undermined (ATMP Regulation, pre-amble 6).

Beneficial Legislation Necessary to Bring New Therapies to Patients

The development of advanced therapies for patients requires large investments in time and money that cannot be done without legislation that offers a clear regulatory situation assuring fair and beneficial market conditions for new therapies.

The full development process of an innovative therapy can easily take 12 to 15 years, including preclinical and clinical safety and efficacy testing. The necessary financial investments often amount to a total of about a billion euro.

Advanced therapies companies can make these large investments only when they have enough certainty about topics like regulatory predictability, market size and market access unhindered by unfair competition. Smaller companies will not attract enough investor money if the market and reimbursement prospects for a product are not good enough.

It is especially important to note that misuse of the Hospital Exemption limits the market size and the potential return on investment for future, centrally approved products. Use of the Hospital Exemption might therefore make it unaffordable to develop a centrally approved product. This means that certain advanced therapies will only remain available for a limited number of patients in a Member State. These local therapies will not be tested for safety and efficacy the same way centrally approved therapies are tested. Furthermore, these local therapies will not become available for all European patients. It is therefore crucial for the development of new advanced therapies that the European Regulation is correctly implemented in all of the Member States, so companies can count on a transparent and harmonized use of the Hospital Exemption in the Europe Union without unwanted and unfair competition, with the aim to benefit all eligible patients in Europe.

National Policies Should Foster Development of New and Safe ATMPs

AAT acknowledges that the implementation of article 28 requires national policy to accommodate the existing national and local healthcare specificities in each Member State. However, these national policies have to fit within the boundaries set by Regulation 1394/2007. National policies should also foster innovation according to the intentions formalized in the ATMP Regulation. In other words, national policies should help foster the development of new and safe ATMPs with approval by EMA, while allowing for strictly non-routine treatments for individual patients.

In a number of countries, the eligibility criteria for the Hospital Exemption are applied liberally, while the exempted products do not have to adhere to the same standards as EMA approved products. This situation undermines the effectiveness of the central ATMP Regulation to ensure the quality, safety and efficacy of advanced therapy medicinal products. Allowing parallel circuits of nationally exempted products with lower standards also presents a barrier for the development of non-exempted products by causing unfair competition. Therefore, the Alliance for Advanced Therapies believes that a harmonized European approach is crucial to bring more innovative therapies to all European patients; therapies that have proven to be safe and effective. The approach should limit Hospital Exemptions to non-routine preparations of treatments under all applicable safety and quality rules. Furthermore, Hospital Exemptions should no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal Product is available.

Ongoing National Implementation Shows Fragmented and Unclear Situation

Article 28 of the Regulation was published in November 2007. The implementation of the Regulation into national legislation is ongoing since then. Quite a few Member States are still developing the required national framework

A first screening of the existing national / guidelines and legislation shows a lack of legal clarity on the interpretation of the criteria in Article 28, resulting in very different interpretations of the Regulation by stakeholders and by Member States as well as large differences in the national implementation of the Regulation. Terminology such as 'preparation on a non-routine basis' used in the ATMP Regulation leaves room for different interpretations. This makes it difficult to establish a uniform interpretation across stakeholders, resulting in the national differences. The Alliance for Advanced Therapies proposes EU-wide harmonization of the definitions and criteria to remedy the problem.

A more detailed analysis shows two groups of issues in the national implementations of the ATMP regulation:

- Interpretation and application of the eligibility criteria for the Hospital Exemption
- National interpretations of the required manufacturing criteria as well as product quality and product effectiveness.

The bullet points below aim to summarize some more specific observations in this respect.

- **Hospital Exemption Applicable Only if All EU Criteria Are Met**
  A number of Member States apply stretched interpretations of criteria like 'custom-made product' and 'preparation on a non-routine basis' from Article 28 of the ATMP Regulation.
  According to the Regulation, products can only qualify for the Hospital Exemption if they meet *all* the criteria mentioned in Article 28. It is therefore evident that ATMPs produced on a regular basis with a standard manufacturing protocol fall under the scope

of the Regulation. A product does not qualify for a Hospital Exemption, just because it is made in a hospital. The use for individual patients or the production in limited series are not enough for a Hospital Exemption either. Even autologous products that are prepared on a regular basis fall under the ATMP Regulation and cannot be exempted only because the product itself is produced from unique material from one person. Therefore, the Alliance stresses that national implementations should only allow for a Hospital Exemption if all of the EU criteria are met.

- **Exempted Activities Should Meet All applicable Safety and Quality Standards**
  The manufacturing and use of an ATMP requires specific attention for safety and quality, especially because of the high level of biological variability, complexity and sensitivity of these types of products. Therefore, national implementations of the Hospital Exemption, should assure that the manufacturing and use of all exempted activities adheres to all applicable safety and quality standards such as GMP, ISO, JACIE and ICH.

Conclusion

The Alliance for Advanced Therapies believes that a harmonized and transparent implementation based on article 28 of European Regulation 1394/2007 is crucial to bring more innovative, effective and safe therapies to all European patients. It is in the best interest of patients to limit Hospital Exemptions to non-routine preparations of treatments under all applicable safety and quality rules. Furthermore, Hospital Exemptions should no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal Product (ATMP) is available.

29 August 2012