



## EBE position paper on the Hospital Exemption

### Introduction

Article 28 of Regulation 1394/2007 on Advanced Therapy Medicinal Products foresees in the implementation of a national procedure to regulate the manufacturing and use of certain non-routine produced ATMPs outside the scope of the Medicinal Product Directive 2001/23. To qualify for this so-called Hospital Exemption (HE), the ATMPs concerned should meet all the following criteria:

- Preparation on a non-routine basis
- Preparation according to specific quality standards (equivalent to those for ATMPs with a centralised marketing authorisation)
- 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

As such, the legislator intends to provide patients the possibility to benefit from a custom-made, innovative individual treatment in the absence of valid therapeutic alternatives (i.e. where there is a clear unmet medical need), under the strict condition that Community rules related to quality and safety are not undermined (ATMP regulation, pre-amble 6).

### Situation assessment

Regulation 1394/2007 was adopted in December 2008 and transposition into local legislation is ongoing. A screening of the currently existing local guidelines and legislation on the provisions from article 28 indicates a lack of transparency and common interpretations among the different stakeholders and Member States. This observation could in part be attributed to the use of vague terminology such as ‘non-routine production’ or ‘industrial preparation’. Overall, it is not clear to what extent the exemption could also be applied for patients with indications that can be effectively treated with an available centrally licensed ATMP, and to what extent the exemption could be (mis)used to maintain existing products on the market beyond the transition period foreseen in the ATMP regulation. For illustrative purposes the currently applied criteria to evaluate ‘preparation on a non-routine basis’ in three EU Member States are compared below:

- Netherlands: Case by case assessment. Autologous products, non-autologous products prepared for a single patient, or ATMPs prepared on a small scale (i.e. maximum 10 treatments for one year) can be considered non-routine by default. Criteria might evolve in the light of experience<sup>1</sup>.
- UK: Case by case assessment based on a set of criteria including the mode of action, the intended use, the manufacturing processes applied and the scale and frequency of the preparation of the

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<sup>1</sup> IGZ procedure voor het verkrijgen van een hospital exemption voor ATMPs (versie april 2011)

specific product. Autologous products are not considered non-routine by default. Criteria might evolve in the light of experience<sup>2</sup>.

- Germany: Established definition. ATMPs which are manufactured in small quantities, and in case a routine manufacturing procedure is applied, variations in the procedure are carried out based on a medical justification for an individual patient. Alternatively, ATMPs which have not yet been manufactured in sufficient quantities to obtain the necessary data to enable a comprehensive assessment are also considered ‘non routine’<sup>3</sup>.

As is shown from these limited examples, the applied interpretations of ‘non-routine preparation’ can be quite diverse between Member States. Such fragmented interpretation leads to uncertainty for ATMP developers and undermines the effectiveness of the legislation.

It is acknowledged that transposition of article 28 requires local policy to accommodate the existing national and local healthcare specificities in each Member State. However, divergent interpretations of the eligibility criteria for the HE presents a barrier for development and use of non-exempted products and reduces the effectiveness of the central ATMP regulation to achieve its three major goals, i.e. to safeguard public health, to provide legal clarity, as well as to stimulate innovation. A careful balance needs to be obtained to provide patients’ access to the best available innovative treatments, in the first instance through evidence-based medicinal products with established safety, efficacy, and quality data or, in the second instance, through an exempted therapeutic option if no such medicine exists. The application of complex, innovative products requires rigorously studied efficacy and safety, and production in an optimal setting to ensure that patients receive the best possible available treatment without being exposed to undue risk. Due to the complexity and sensitive nature of ATMPs, small changes in the handling or production process might drastically impact the product quality, safety and efficacy<sup>4</sup>.

The tendency towards an open interpretation of the exemption is also presented in a series of recent publications in which the authors refer to the exemption as the preferred route for certain types of ATMPs<sup>5, 6</sup>. As such, the exemption would become the main rule under the premise that a national controlled regime is considered more appropriate for certain innovative treatments than the centralised procedure. Whereas it is recognised that an important number of innovative treatments find their roots in the hospital and academic environment, for which the scientific research performed at these institutions is of invaluable importance, it is also acknowledged that medicinal product development is not - and should not - be the primary interest of these institutions. As such, the legislator needs to safeguard the incentives to translate innovation from bench to bedside. If not applied carefully, the implementation of the hospital exemption might

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<sup>2</sup> MHRA ATMPs guidance. Guidance on the UK’s arrangements under the hospital exemption scheme. Annex B – Non-routine guidance.

<sup>3</sup> AMG § 4b.

<sup>4</sup> Van Wilder P. Advanced therapy medicinal products and exemptions to the Regulation 1394/2007: how confident can we be? An exploratory analysis. *Frontiers in Pharmacology*. Perspective article. 14 February 2012.

<sup>5</sup> Buchholz J, Sanzenbacher R, Schüle S. The European Hospital Exemption Clause – New Option for Gene Therapy? *Human Gene therapy* 23:7-12 (January 2012).

<sup>6</sup> Hidebrandt M and Sethe S. Caught in the Gap: ATMP manufacture in Academia. *ISCT Vol 19 No 1*, January 2012.

result in a parallel circuit of national exempted products with different and often less stringent criteria and rules as those applied by the Committee of Advanced Therapies.

### Conclusion

The biopharmaceutical industry appreciates and supports the therapeutic option for certain patients to receive treatment with a customised innovative product, particularly in those situations where the disease occurs so rarely that full development and validation of the required therapy is often not feasible. However, the HE should be correctly applied and not turn into a parallel circuit for small-scale, locally produced ATMPs competing with centrally authorised products. **As a general policy, hospital exemptions should no longer be allowed in those situations where a fully validated, centrally approved ATMP is available for the same indication in the same patient population.** At this moment, there is no European-wide legal certainty on this point. If not addressed, this might lead to undermining the ATMP regulation and ultimately the full clinical development and regulatory control of innovative treatments with important consequences for the patients as well as jeopardising investment by the cell therapy industry as a result of lack of clarity in the regulatory framework.

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