



COMMENTARY

The puzzling situation of hospital exemption for advanced therapy medicinal products in Europe and stakeholders' concerns

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Background

In Europe, advanced therapy medicinal products (ATMPs), including cell and gene medicinal products [1], tissue-engineered products [2] and combined ATMPs [2], are governed by Directive 2001/83/EC [3] and Regulation 726/2004 [4], amended by Regulation 1394/2007 [2], which sets specific rules concerning their centralized marketing authorization (MA), supervision and pharmacovigilance.

Nevertheless, ATMPs not intended to be marketed and not industrially prepared are beyond the scope of Directive 2001/83/EC, according to article 28 of Regulation 1394/2007. This is commonly called “hospital exemption” (HE) and is restricted to any ATMP “which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.” Member States must ensure that the manufacture of ATMPs under HE is authorized by the competent national authority and that traceability, pharmacovigilance and specific quality standards are equivalent to those applying to ATMPs granted centralized MA.

HE requires transposition into national laws. Some European countries have already done this, with Finland, United Kingdom and Germany being

the first. The difficulties associated with the interpretation of HE has led them to setting sometimes-divergent pathways and rules [5].

Primary issue arising within the scope of HE

Directive 2001/83/EC does not specify what is meant by “industrial process,” nor does the regulation specify the meaning of a “custom-made product.” Nevertheless, some countries have defined those terms. In the United Kingdom, the Human Tissue Authority [6] has defined “custom-made” as “using a one-off formulation or a formulation that has been tailored to the individual patient and prepared within the same hospital” and “An industrial process would generally take place in an external facility and not within the same hospital.” This is a specific interpretation; the process (industrial or not) is the most important aspect, not the location, because the same process can take place in facilities inside or outside hospitals. In fact, HE clause (Regulation 1394/2007) is in effect irrespective of the type of manufacturer.

Different interpretation of HE in European Countries

Countries have interpreted the definition of “non-routine basis” differently because the European

Commission has never specified any particular number to constitute “non-routine.” The United Kingdom takes the view that “it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and non-routine production” [7]. The Netherlands has chosen a concrete definition of “non-routine basis,” allowing the infusion of one product for a maximum of five patients and fewer than ten patients a year [8]. The German Medicinal Products Act [9] has defined ATMPs prepared on a non-routine basis as those “medicines which are manufactured in small quantities, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient, are carried out, or which have not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available.” In the case of Finland [10,11] France [12], Spain [13] and Portugal [14], there are no provisions for any specific quantity.

Regarding the entity holding the license, most countries grant HE to ATMP manufacturers, and in Spain and Portugal the license is given to hospitals. In Spain the licence is irrespective of the manufacturer. Therefore, if several Spanish hospitals were interested in using an ATMP produced by a single manufacturer, each hospital should submit a dossier equivalent to a Common Technical Document.

Although most countries require Good Manufacturing Practice (GMP) as the quality standard applicable under the HE scheme, there are some differences. In the United Kingdom, a qualified person is not required [15]. In Germany, “person identity” of the manufacturer is not necessary. Although GMP is required in the Netherlands, France and Spain, there is some degree of flexibility.

When does HE apply?

Perhaps the most important issue regarding HE is the situation or circumstances in which it applies with marked differences among countries. In the United Kingdom, the HE scheme “does not apply to ATMPs that will be authorised under the ATMP Regulation ... nor does it apply to ATMPs supplied as investigational ATMPs for use in a clinical trial (CT) [15].” Nevertheless, the United Kingdom established a second scheme for unlicensed products by implementing a procedure to supply “specials” (ATMPs) under Article 5(1) of Directive 2001/83/EC that, in contrast to HE, allows import and export of unlicensed ATMPs. The Netherlands applies HE for patients ineligible for a CT (as in compassionate use) or when the required product falls outside the

specifications. In Finland, quality (but not non-clinical) data are required, allowing small-scale clinical use while non-clinical studies are carried out to facilitate a later CT. However, in Spain it is only possible to apply for HE when efficacy and safety have been demonstrated, and quality, non-clinical and clinical data must be provided. Here HE is considered as an alternative to MA for products non-industrially manufactured and not intended to be marketed, but not as an alternative to CTs. In Germany HE may be applicable to facilitate or accompany a CT (not as an alternative) but also for conveying products in a preliminary “non-routine status” on their way to centralized MA. In France, ATMP under HE require same clinical trials than other medicinal products and in Portugal there are no provisions regarding when HE applies.

On the subject of the duration of the authorization under HE, in Netherlands the product-specific license lasts for 10 batches or for 1 year, whereas in Germany there is no precise product-specific license period. In the case of Finland, the license for non-industrial manufacture of ATMPs may be granted for a fixed or indefinite term, in Portugal is granted by one year being renewable and in Spain authorization is initially granted for 3 years and then for 5 years in successive renewals.

The concerns of the affected stakeholders

Small and medium enterprises and non-for-profit organizations (mainly universities and public hospitals) are leading the clinical development of ATMPs in Europe, with great variability among countries. In Spain and Italy the role of industry has been minimal, whereas in the United Kingdom, Germany, France, Sweden and Denmark, it has been quite important [16]. These differences have probably been instrumental in the way National Authorities have implemented HE. Here there are several examples. Germany has been the leading country in granting products under HE, most of them in the German market before the entry into force of the Regulation 1394/2007/EC. This has allowed those companies that have not applied for or have not been granted a European MA to continue their activity there. Although the United Kingdom was one of the first countries regulating HE, the majority of the authorizations to manufacture and supply unlicensed ATMPs have been granted under the United Kingdom’s “Specials” scheme. This scheme permits import and export activities, affording competitive advantage for the United Kingdom in comparison to other countries. Spain, with unlicensed ATMPs included in the Common Services Portfolio of the National Healthcare System as standard of care without

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