Orphan Drug Development Guidebook

Building Block E135

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Magisterial hospital preparations – Hospital Exemptions (HE)
References	https://health.ec.europa.eu/system/files/2016-11/07_1_pc_atmp_2013_0.pdf https://alliancerm.org/sites/default/files/ARM_position_on_HE_final.pdf
Description	In the EU, ATMP products are governed by Regulation 1394/2007 on advanced therapy medicinal products ("ATMP Regulation"). The cornerstone of the Regulation is that a marketing authorisation must be obtained prior to the marketing of ATMPs. The evaluation of these products is led by a specialised committee within the European Medicines Agency (EMA) i.e., by the Committee for Advanced Therapies ("CAT") who prepares a draft opinion before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion and the authorisation is granted by the EU Commission. Article 28 of the ATMP Regulation also empowers Member States to permit the manufacturing and use of certain non-routine produced advanced therapies that have not been authorised by the Commission under certain conditions (so-called "Hospital Exemption") 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 (country by country variability on the actual meaning/number of preparations/administrations) • Preparation according to specific quality standards (equivalent to those for ATMPs with a centralised marketing

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	authorisation) • Use only within the same Member State • Use only 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.
Category	Regulatory Building Block
Geographical scope	European The hospital exemption rule can be applied in each Member State of the European Union individually. Member States should provide national procedures and control measures after implementation into their national law.
Availability	Only applicable to ATMPs (for Rare and non-rare Diseases)
Scope of use	Hospital exemption can only be applied for custom-made ATMPs used in a hospital setting for a specific patient.
Stakeholders	Hospital pharmacies, hospital pharmacists, medical practitioners, facilities that allow medicinal preparation according to specific quality standards equivalent to those for ATMPs with a centralised marketing authorisation.
Enablers/ Requirements	Hospital pharmacies, hospital pharmacists, medical practitioners, facilities that allow medicinal preparation according to specific quality standards equivalent to those for ATMPs with a centralised marketing authorisation.

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Output	An Advanced therapy medicinal product which is prepared on a non-routine basis according to specific quality standards, and is 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.
Best time to apply and time window	Not applicable (country by country variability in terms of data requirements)
Expert tips	The hospital exemption status should be considered very cautiously and really limited to very specific cases. PROS • The hospital exemption's obvious advantage is that patients can receive much needed ATMP treatments in situations when no product has been authorised. Hospital exemptions also allow patients to benefit from ongoing clinical research, particularly in areas of unmet medical need. CONs • 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 as it contradicts the principle of the Art.28 of the ATMP Regulation. • Hospital exemption products can only be used within the respective EU member state (no exportation is permitted under this provision). • At this moment, there is no European-wide legal certainty on this point. • the use of hospital exemption instead of the central marketing authorisation to the market deprives large groups of patients across Europe of the benefits of therapy, while potentially compromising: ○ quality: in some counties "GMP like" rules will necessarily lead to lower quality of the products

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	than standard GMP. ○ safety: the risk is to authorize a large number of hospital exemptions corresponding to the same type or to very similar products, each site being authorized nationally based on proper manufacturing technology. This situation could question the safety issues as the multiplicity of the production sites using similar but slightly different manufacturing processes is a less safe situation compared to a limited number of manufacturing sites with a unique standard manufacturing technology for which audits and inspections are more frequent; on thew other hand, the processes elaborated for a very low number of patients are always performed in less closed systems (increased risk of contamination) with less automated solutions (decrease of robustness and reproducibility) of the ATMP. • lack of efficacy evidence. • access to the therapy is not ensured for patient. • negative signal for industry and investors to invest in R&D. 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.