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Advanced therapies

Terapias avanzadas

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We live in exciting times for pharmacology. In the last few years, the lives of many patients have been changed by the use of new therapeutic strategies for the management of cancer or rare diseases. Specifically, the emergence of Advanced Therapy Medicinal Products (ATMPs) has led to realistic expectations regarding the curative treatment of diseases such as acute refractory leukemia or diffuse refractory large cell lymphoma. Likewise, promising gene therapies are now available for the treatment of previously devastating orphan diseases, such as spinal muscular atrophy. Research and development on ATMPs is thriving. Some of the factors catalysing this situation have arisen from a favourable and successful - regulatory framework. This framework includes the ATMP Regulation, which ensures their development while providing human health with a high level of protection. It also makes certain that the EU as a whole benefits from a common, harmonized, and safeguarded ATMP development policy. The framework also includes the Priority Medicines (PRIME) program launched by the European Medicines Agency (EMA) to enhance support for the guided rapid development of promising medicinal products, such as ATMPs, that target unmet medical needs.

On the one hand, Regulation (EC) No 1394/2007¹ subjects ATMPs to the same principles as other medicines; pre-marketing authorization, demonstrated quality, safety and efficacy with a positive risk-benefit ratio, and post-authorization pharmacovigilance. On the other hand, to guarantee these harmonized requirements and assessments throughout the EU, this regulation states that ATMPs have to undergo the centralized authorization procedure coordinated by the EMA and granted by the European Commission simultaneously for the entire EU. In addition, this regulation led to the creation the Committee for Advanced Therapies (CAT) to assess, certify, and classify these ATMPs. Classifying a cell-based treatment as a medicinal product or otherwise is based on the degree of manipulation cells have undergone and whether or not they retain their original function. The first concept, substantial manipulation, has been elucidated in the light of scientific knowledge. However, it can be difficult to determine whether a cell, which is often pluri-potent, will perform the same essential function in the recipient as in the donor. The certification procedure cited in the

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legislation is really an instrument developed as an incentive for small and medium enterprises that are often involved in the early stages of ATMP development, but that lack the resources to conduct clinical trials. This certification procedure is an attempt to ensure that preclinical development and product quality are correctly aligned with what would be expected regarding the regulatory development of a product. This measure makes a lot of sense, because the development of this type of medicinal product often begins in academic groups or in micro-, small-, or medium -sized companies. In fact, the scope of the regulation includes industrially prepared ATMPs or ATMPs manufactured by a method involving an industrial process. However, the regulation itself excludes from its scope ATMPs that are prepared on a non-routine basis according to specific quality standards, and that are 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. This clause is what is known as the hospital exemption clause or hospital exclusion clause and is the source for the Spanish national regulation of non-routine produced ATMPs.

In 2017, the European Commission published the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products². It states that products manufactured and administered under Hospital Exemption must meet quality standards, that they will be authorized by the competent authority of each Member State (i.e. the AEMPS in Spain), and that authorized centres must ensure national traceability and pharmacovigilance requirements as well as specific quality standards that are equivalent to those offered at the EU level for ATMPs that follow the centralized authorization procedure.

In Spain, these aspects were addressed by Royal Decree 477/2014 of June 13, which governs the authorization of ATMPs that have not been industrially manufactured. The procedure for requesting authorization requires the presentation of a dossier that documents -according to ATMP specificities- the pre-clinical, clinical, and quality data needed to assess the risk/ benefit ratio in order to ensure that it is positive. This implies that the research team has data obtained from clinical trials that support a provisional positive risk/benefit ratio, and that while knowledge about the drug is increasing, patients who otherwise could not be treated have access to the drug.

Authorization, as mentioned, is granted to a hospital in the name of its Head executive, but the medication does not have to be manufactured in that hospital because third parties are permitted to manufacture it. Thus, the authorised centre administers the therapy and is able to manufacture it, or it can be manufactured by a third party providing it has transferred the product quality data to the hospital that has presented the authorization request. Authorization of use has an initial validity of 3 years and can be renewed periodically; however, authorisation may be subject to annual review. The natural route for an ATMP to be granted authorisation of use is via a centralized marketing procedure, since it is

understood that, if there is sufficient evidence in support of its quality, efficacy and safety, any patient who needs it can access it without such access being restricted to the hospital of origin.

In Spain, the hospital exclusion clause is of special relevance because there is a powerful research network with an excellent cleanroom infrastructure thanks to the public investment and funding of independent clinical research on ATMPs that supports research groups such as those affiliated with the Cell Therapy Network (TERCEL) of the Instituto de Salud Carlos III (Carlos III Health Institute). This infrastructure can and should provide the clinical trial system, as well as support the manufacturing of ATMPs with authorization for use.

Another determining factor in the availability of ATMPs is the PRIME program introduced by the EMA. This voluntary program is based on improved interaction and early dialogue with drug developers. It can offer great therapeutic advantages over existing treatments or benefit patients without treatment options. PRIME relies on the current regulatory framework and the tools already available, such as scientific advice and accelerated evaluation. The aim of early dialogue with drug developers is to improve the design of clinical trials and to ensure that patients only participate in trials designed to provide the needed information. To be accepted into PRIME, a medication must demonstrate its potential based on early clinical data. Of the 45 ATMPs currently included in PRIME, there are 21 that cover hemato-oncological indications, solid tumours, haemophilia, and rare and ultra -rare diseases. As an example of the relevance of the PRIME scheme, two ATMPs (Yescarta and Kimryah) that met the PRIME criteria were granted marketing authorisation in 2018.

Finally, 2018 saw the approval of the Plan for Advanced Therapies Management in the Spanish National Health System: CAR Medications³. This plan established an organizational and healthcare model to achieve the optimal use of these medicinal products and ensure fair, safe, and efficient access. It is important to acknowledge that Hospital Pharmacy specialists, as part of medical teams and researchers, play a key role in sustaining this organizational model and in providing quality healthcare. They ensure the timely selection of the most appropriate medicinal product for the right patient under the highest quality standards throughout the process⁴. In summary, based on a regulation that empowers and encourages the industrial and non-industrial development of ATMPs, together with vibrant research activity and a market access plan within the Spanish National Healthcare System, we will witness the arrival of truly innovative medicinal products that will benefit all our patients.

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