

THE HOSPITAL EXEMPTION

INCREASING ACCESS TO INNOVATION AND
LOCAL PRODUCTION



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In 2007, the European Regulation [EC] No 1394/2007 on Advanced Therapy Medicine Products (ATPM) enabled an alternative regulatory pathway known as the Hospital Exemption (HE). The HE pathway has significantly improved patient access to these innovative therapies within the European Union. Currently, it is undergoing revision as part of the EU pharmaceutical legislation reform. Therefore, this paper aims to contribute to strengthening this useful instrument at a critical juncture.



Advanced Therapy Medicine Products (ATPM) have revolutionized the pharmaceutical field (1), and they represent an opportunity for individual treatments or smaller groups of patients. However, the most challenging aspect is for present and future innovations to respond to many unmet clinical needs. Moreover, patient access is a critical issue for these innovative products, many of which are developed in public clinical or academic settings (2). In these contexts, a hospital exemption (HE) clause was legally introduced as a potential solution in the EU to accommodate this reality into existing regulatory frameworks for Member States (3). A proven appropriate instrument with the ability to expand access to innovation to all possible contexts and to strengthen R&D inside public and academic spheres.

"In-house" manufacturing of ATMPs in these centers can be carried out by applying this clause under Article 28 of Regulation (EC) 1394/2007 (4). The HE allows some ATMPs to follow a different pathway than the EMA centralized market authorization (MA). Conditions that must be fulfilled under Art.28 include preparing an "individual medical prescription for a custom-made product for an individual patient", done "on a non-routine basis". Additionally, manufacturing of these ATMPs should be authorized by each European Union member state, ensuring that traceability, pharmacovigilance, and quality standards are the same as for the rest of ATMPs.

Both authorities and experts have emphasized the interesting possibilities this approach opens up for R&D in advanced therapies (5,6), although there are still regulatory barriers and differences among various stakeholders. From a clinical perspective, the possibility of CAR-T cell production within the hospital itself offers advantages related to the process that directly benefits the patient. It reduces waiting times, logistical burdens, minimizes the risk of identification errors or delays in availability, promotes better coordination among the teams and individuals involved in the process, and, at the same time, allows for the constant improvement of the overall process through the practical clinical experience (7-9).

SPANISH MODEL: A CAR-T SUCCESS STORY OF PUBLIC INTEREST

Spain implemented Article 28 of Regulation (EC) 1394/2007 in 2014 with the Royal Decree 477/2014, which regulates the authorization of advanced therapy medicinal products of non-industrial production (10), referring to those prepared on a non-routine basis (occasionally), following specific quality standards, within a hospital institution and under the exclusive professional responsibility of a registered physician, for the purpose of fulfilling an individual medical prescription.

The Hospital Clínic of Barcelona became a pioneer in the development of the ATMP ARI-0001, a CAR-T therapy. In 2013, a project initiated with public funding enabled the preclinical and clinical development of the first CAR-T platform against acute lymphoblastic leukemia (ALL) at this center (8). The primary goal was to treat patients with ALL within the public healthcare system (11). The hospital had extensive research experience dating back several years, particularly related to their proprietary monoclonal antibody known as A3B1 (11,12). The process culminated in 2021 when ARI-0001 received authorization from the Spanish Agency of Medicines and Medical Devices (AEMPS) under the HE approval pathway for patients over 25 years of age with relapsed/refractory ALL (13). It also received manufacturing approval, with accreditation of the Good Manufacturing Practices (AMP) Cell Production Facility, among other requirements such as a Pharmacovigilance Plan (9).

This development allowed patients without other therapeutic options to be treated without commercial interest. Innovation in Hospital Clínic of Barcelona has not stopped there: the AEMPS is already reviewing a second hospital exemption for another CAR-T ARI0002h for patients with multiple myeloma (14). It is essential to highlight that the Clínic approach has no commercial interest and has also included an access approach that transcends the limits of the hospital setting, developing licensing strategies with third countries¹, as well as improving access for patients across other hospitals in Spain(15). It is, therefore, a successful example of local production, collaborative network development, and technology transfer practices constructed around the public interest that can serve global access interests.

HE IN EUROPE: TIME TO IMPROVE AND SAFEGUARD LOCAL PRODUCTION, INNOVATION, AND THE RIGHT TO HEALTH

In this sense, the above-stated Spanish Model is a good example to build upon the HE clause to harmonize it across the EU so that all patients can equally access innovations, with equal access to high-quality, affordable, and safe medicines. This will contribute to improving the current lack of homogeneity of the HE in the Union, with Member states implementing it with a high degree of variability in terms of GMP compliance, clinical data requirements, eligibility, or the scope itself of the HE(3). The understanding of the Spanish Model is that the HE should be an intermediate step toward centralized MA(16) In fact, the CAR-T ARI-0001 has received PRIME designation by the EMA, for an accelerated review, which makes the Hospital Clínic the first academic institution to have ever achieved this designation (17). Although the Spanish Model increases the workload of the institutions, as there are high standards to be fulfilled and some are unfamiliar regulatory or production standards (15), it allows it to attain the necessary clinical data to continue toward centralized MA while also promoting the development of both manufacturing requirements and regulatory expertise in these institutions.

The HE, in this way, creates an important ecosystem with two relevant outcomes: on the one side, increased patient access to ATMPs developed in proximity to clinical practice that could be otherwise not available for them; on the other side, it promotes innovation, R&D and regulatory capabilities at academic and health institutions. This occurs while lowering the cost by two-thirds of that of a commercial CAR-T therapy (15), which could potentially help to decrease the excessively high prices in the sector. It is, therefore, a critical case of local production created by and for the public interest. In this sense, it is also aligned with the EU's strategic autonomy project and should be seen as a complementary approach to centralized MA. The coexistence of both modalities is of interest to the patients and public health systems.

Academic ATMPs appear thus not only a priority for the EU, but also for Spanish Government, which has made investments through the EU-funded Strategic Projects for Economic Recovery and Transformation (PERTE) to develop clinical research projects geared to the development of medicines at an academic level, platforms to support R&D transfer and manufacturing capacity within a hospital network (18).

It has also brought a change of paradigm in Spain in terms of manufacturing and management of ATMPs within the public sector that has fostered the development of the national network of advanced therapies in the national health system along with national policy plans (19). In this regard, the *National Plan to approach Advanced Therapies in the National Health System: CAR medicines* states that its primary objective is “to organize in a planned, equitable, safe and efficient use of CAR medicines, currently CAR-T, in the national health system, as well as to promote public research within the public system, as well as to promote the own and public manufacture of these medicines in the academic field, under conditions that guarantee quality, safety and efficacy standards” (20).

Furthermore, it is worth noting that the Spanish government co-sponsored the 2021 WHA Resolution 74.6 Strengthening local production of medicines and other health technologies to improve access (21), which urges Member States to support the establishment of “quality and sustainable local production of medicines and other health technologies that follows good manufacturing practices” with financing mechanisms, transparency, and North-South cooperation.

THE WAY FORWARD: THE PHARMACEUTICAL DIRECTIVE

In 2012, the European Commission conducted a public consultation in which authorities, academia, and industry provided their opinions on European regulation in advanced therapies. While the scientific community perceives this as a positive legal instrument that allows hospitals to innovate in the public domain, the business sector views it as more of an inconvenience and a disincentive to their R&D (22). Now, the EU pharmaceutical legislation is under review. This process must serve to improve the HE instrument instead of diluting and shredding what has been proven to be successful. In this regard some critical aspects have to be introduced:

01. Patient access

The HE is an instrument to be safeguarded as it ensures patient access to newly developed products and opens alternatives for R&D manufacturing. Moreover, products under HE approval with proven quality, safety, and efficacy should continue to be available for patients regardless of the entry of other products with marketing authorization approvals. Social return of public investments, quality, and continuous improvement should be criteria for HE products to continue their use, as elements blocking access are diverse, ranging from availability to economic reasons.

02. Spanish experience

The Spanish experience is a good example, with many requirements already in place, and good results should serve as a basis for further improvements. In this regard, the HE should require equivalent data entry requirements as centralized MA in terms of preclinical and clinical data and manufacturing (GMP compliance) and quality. An EU-wide registry should be put in place to track all HE products at a European level, in a way that can strengthen collaboration and transparency among hospitals and non-profits. Network collaboration needs to be reinforced for knowledge sharing of process standards but also for the purpose of international clinical trials.

03. European support

There must be strong support at the European level to lead to authorization by the EMA to ensure access across the EU. Competent authorities should provide scientific advice to academic and nonprofit institutions, allocating the resources needed for this purpose and reinforcing the current PRIME pilot. These institutions with non-commercial profiles will need support not only for different phases of clinical trials but also for the regulatory and industrial procedures. Therefore, funding should be available at different national and regional levels. For this purpose, the waiver of market exclusivities should be considered to avoid additional barriers to expanding access across the Union.

04. Reimbursement and transparency

Transparency around public funding of HE and reimbursement price should respond to social return criteria. Final prices should be made public for all medicines, especially those with public support. Publicly funded academic ATMPs should be prioritized to expand their adoption when appropriate. Furthermore, supports should be in place to include in the registry transparent licensing agreements, such as those used by the Medicines Patent Pool.

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