POLICY COHERENCE BEYOND THE RARE DISEASES RESOLUTION

A PRIORITY FOR SPAIN AND AN OPPORTUNITY FOR GLOBAL EQUITABLE ACCESS TO MEDICINES

The announcement of Spain's decision to co-sponsor a resolution on rare diseases to be addressed at the upcoming World Health Assembly reflects the Ministry of Health's initiative to increase its international presence. This initiative coincides with the negotiations on the European Pharmaceutical Legislation, which addresses, among other topics, incentives for developing orphan drugs (medicines for rare diseases) in the EU. Finally, it also aligns with the development of a national ecosystem to develop and commercialize affordable advanced therapies, increasingly used to treat rare oncological diseases. This creates an opportunity to align national and international pharmaceutical policies to expand equitable global access to medicines for rare diseases.

This analysis summarizes some of the challenges arising from the public policies implemented to incentivize the development of medicines for rare diseases. Through a brief case study on CAR-T therapies, it justifies the need for policy coherence in national and international pharmaceutical policies that improve transparency and global equitable access to orphan drugs.

1. What Are Rare Diseases? (1)

Rare diseases are those that affect a very small number of people in a specific territory. Their low prevalence often makes them unattractive for the pharmaceutical industry to invest in research and development (R&D) for products to treat or diagnose them, as the return on investment would be too small.

The categorization of "rare disease" is not standardized globally, nor does it encompass a specific group of diseases:

- In the United States, rare diseases are defined as conditions affecting fewer than 200,000 people in the country.
- In Japan, diseases affecting fewer than 50,000 people are considered rare.
- The European Union's Orphan Drug Regulation defines rare diseases as those that are "life-threatening or chronically debilitating" and affect no more than 5 in 10,000 people in the EU.

- A recent editorial in The Lancet Global Health defined rare diseases as those affecting 1 in every 2,000 people in any WHO region(2).

Some definitions of medicines for rare diseases also include economic viability as a secondary criterion to designate medicines as orphan. The EU legislation theoretically allows the withdrawal of an orphan designation if the drug no longer meets certain criteria (e.g., if the drug becomes sufficiently profitable). However, such provisions do not appear to have been enforced.

2 · Pharmaceutical Innovation for Rare Diseases: A model with significant weaknesses (1)

To address the lack of interest from the pharmaceutical industry, different countries have developed public policies to incentivize R&D for rare diseases. These policies include increased public R&D funding, tax breaks for clinical research on rare diseases, regulatory fee waivers, and/or regulatory advice to developers. Furthermore, market exclusivity extensions, which enable medicines for rare diseases to be marketed at very high prices, serve as an attractive incentive for the pharmaceutical industry.

While treatment options for many rare diseases have expanded, these extensions of market exclusivity have generated chronic systemic issues that raise questions about the sustainability of the system:

- **Unaffordable prices:** Orphan drugs are often launched at extremely high prices, making them inaccessible to many healthcare systems. Market exclusivity grants developers an additional monopoly period (seven years in the U.S. and ten years in the EU), preventing the entry of generics, biosimilars, and other therapies for the same indication. This leads to inflated prices, which are rising faster than those of non-orphan drugs.

- **Indication stacking:** Drug sponsors can obtain multiple orphan designations for a single drug, each with its own exclusivity period, extending the monopoly for decades. Between 1983 and 2017, at least seven orphan drugs achieved 20 or more years of monopoly by stacking orphan designations(3).

- **'Salami Slicing':** To obtain a higher number of orphan designations for a single drug, some manufacturers subdivide diseases into smaller categories, with studies showing that the indications with prevalences slightly over the threshold to be considered rare are more likely to be subdivided, and that treatments for those indications had more chances to be sold off-label, in order to expand the patient base.

- **Neglected Diseases:** The industry has focused primarily on developing treatments for oncological conditions that allow for multiple orphan designations and expansion of patient base through off-label use, while other rare, ultra-rare and neglected diseases remain unattended.

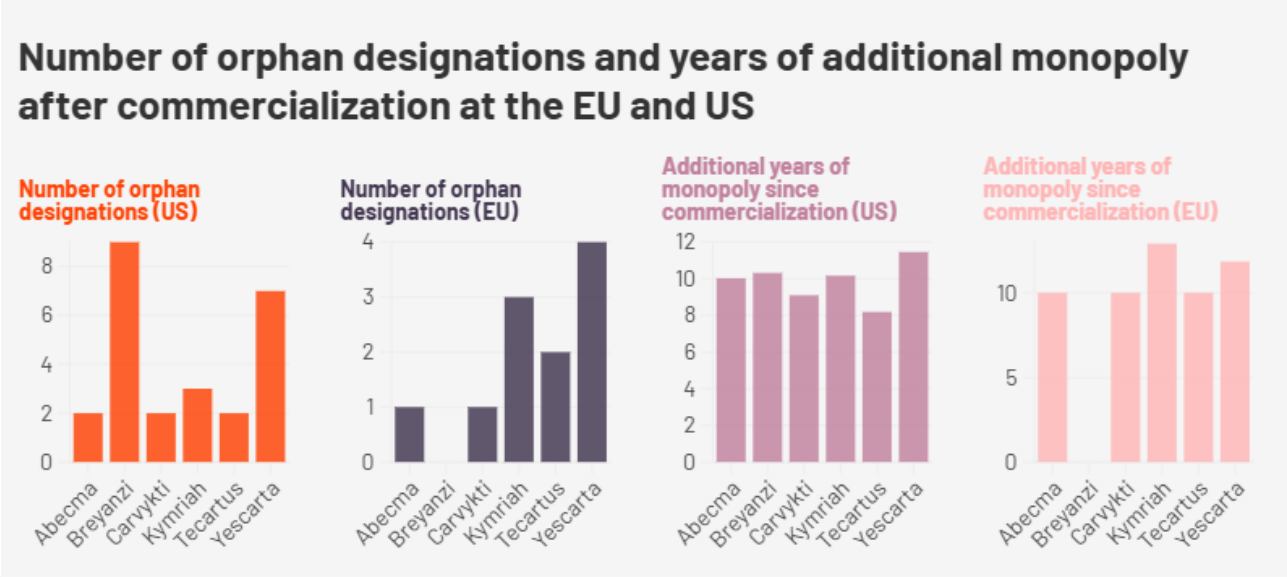
- **Systemic Issues:** In addition to these disease-specific challenges, the orphan drug market is plagued by systemic issues tied to the pharmaceutical innovation model. These include a lack of transparency in the real prices paid by countries, opacity in the actual costs of development and production, and limited access in low- and middle-income countries.

Although these issues are widely documented in the academic literature, the current review of the European Pharmaceutical Legislation proposes incentives for orphan drugs that extend the monopoly to a maximum of 13 years, though it would prohibit stacking orphan designations. However, it still does not require greater transparency, affordable pricing, or justification that the indication in question lacks economic viability in order to receive the incentives.

3 · Case Study: CAR-T Therapies as Orphan Treatments

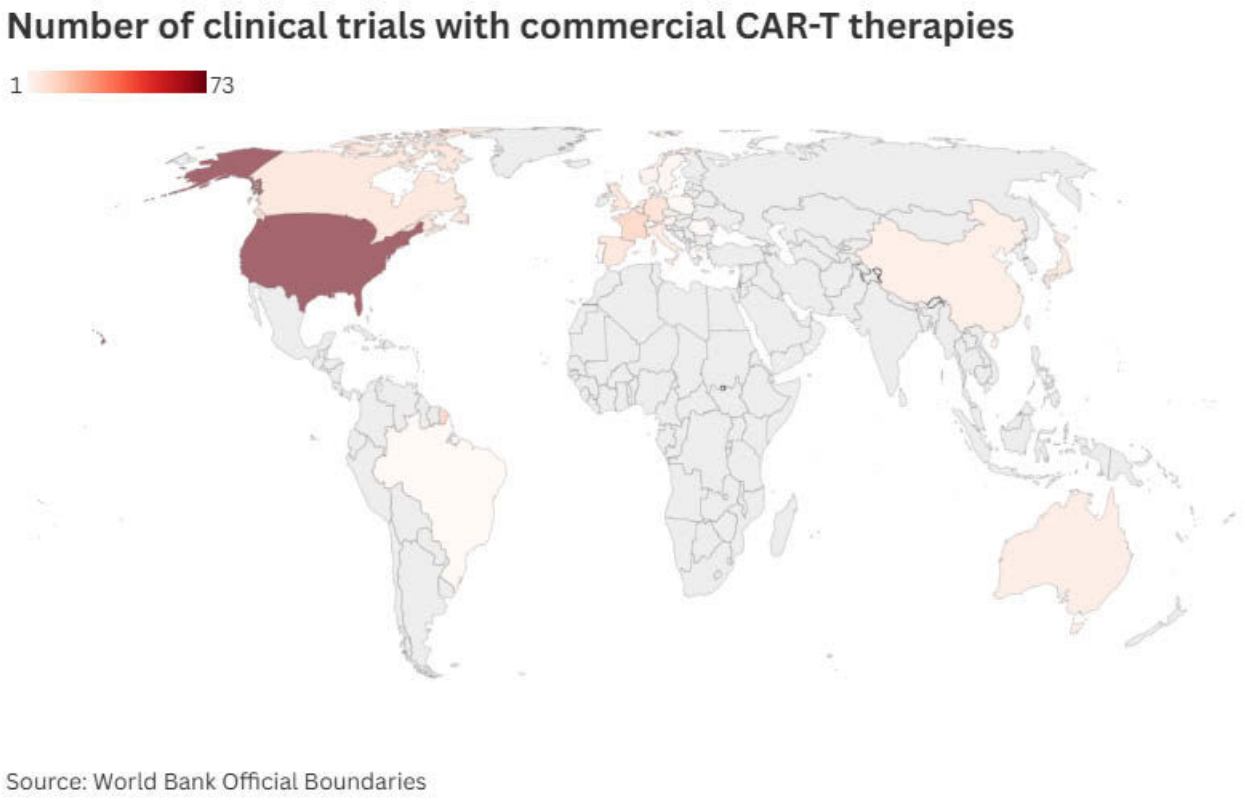
CAR-T therapies are a type of advanced therapies that have been instrumental in improving the treatment of various types of rare cancers. According to data from the FDA(4) and EMA (5), **all CAR-T therapies approved by both agencies are designated as orphan drugs** (with the exception of Breyanzi in the EU, where three orphan designations were voluntarily withdrawn by the sponsor (6)).

In addition to monopolies granted by patents, and other regulatory incentives, CAR-T therapies benefit from **an average of 10.14 additional years of exclusivity in the U.S. and 10.96 years in the EU, thanks to orphan drug incentives**. Each therapy has between **9 and 2 orphan designations in the U.S. and between 4 and 1 in the EU.**



When compared to other orphan drugs in the U.S., CAR-T therapies enjoy, on average, 1.45 more years of monopoly and 2.49 more orphan designations. **The lack of public data makes comparisons in the EU impossible.**

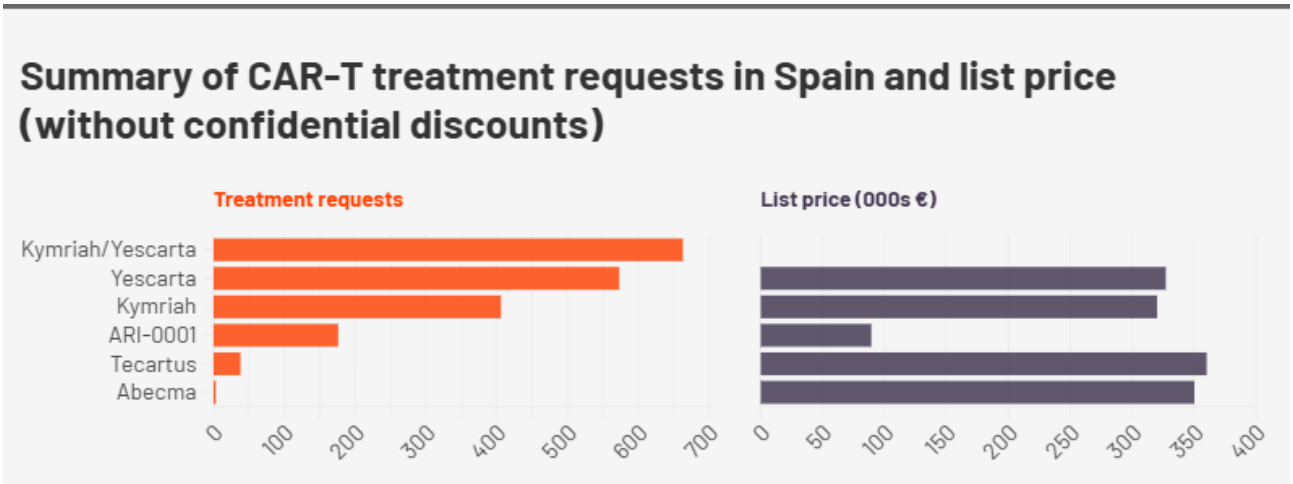
Global access to CAR-T therapies is difficult to assess in terms of registration and availability in different countries. However, a preliminary analysis of clinical trials conducted for commercial CAR-T therapies paints an unequal picture: the vast majority of trials have been conducted in the U.S., Canada, Europe, Japan, Australia, and China. **While hosting clinical trials does not guarantee subsequent access to treatments,** it provides an indication of the geographic focus for market entry by pharmaceutical companies.



In Spain, the development of advanced therapies has become a health and industrial priority. The country has invested in building a robust network of preclinical and clinical research in advanced therapies within the public sector, using instruments like the **Terav Network and the Strategic Projects for Recovery and Economic Transition (PERTE in Spanish) for Vanguard Health**. Furthermore, the recently created public-private pharmaceutical company, Terafront Farmatech, aims to develop, manufacture and commercialize advanced therapy medicines with sustainability and accessibility within the National Health System (NHS) as foundational principles(7).

According to the Plan for Addressing Advanced Therapies in the NHS, in Spain there have been a total of 1,859 CAR-T treatment requests between March 2019 and June

2024, with a growing trend in annual requests(8). The prices for these therapies in the U.S. are around **$400,000 per treatment**, while in Spain, before undisclosed discounts negotiated with the industry, prices range between **€360,000 and €320,000**(9–12). The notable exception is ARI-0001, developed by the Hospital Clínic of Barcelona, costing **€89,270 per treatment(10).** This therapy serves as one of the best examples of Spain's R&D model for advanced therapies. Its use has been authorized under the Hospital Exemption clause for cases of relapsed or refractory B-cell Acute Lymphoblastic Leukemia in adults, a type of cancer classified as rare (13).



While multiplying the number of treatment requests by the stated prices would yield a cost of approximately €348 million (excluding combined Kymriah and Yescarta treatments for which prices remain undisclosed), the Ministry of Health refuses to publish the prices after the discounts provided by pharmaceutical companies, making it impossible to determine the true cost of these therapies for the public health system.

This case study shows in two ways, that national and international pharmaceutical policies have an interconnected impact that escapes national borders. Firstly the lack of net price transparency (after signing confidential discounts with the industry) not only hinders accountability in Spain (as it impedes to know how much public money is spent on these therapies), but also lead to higher costs in other countries, including many low- and middle-income countries that use Spain's public prices as a reference. The same way that secret pricing mechanisms in other countries indirectly drives up costs in Spain.

Secondly, the EU's market exclusivity incentives to develop orphan drugs, have increased the cost of medicines to EU member states, affecting the sustainability of healthcare systems. However, these rules may also hinder Spain's strategy to develop affordable advanced therapies nationally. Under the current EU legislation, and also in the proposed reforms, **ARI-0001 could not be marketed in Europe until the exclusivity period for Tecartus (estimated until 2030) ends**, unless certain exceptions are met, as both orphan treatments share the same indication and market exclusivity incentives impede having two orphan drugs for the same indication(14).

4 · Policy Coherence Beyond the Rare Diseases Resolution: Leadership for Equity

Throughout this document, we have described how national and regional policies create systemic failures that hinder equitable global access to orphan therapies. If the problems are systemic, solutions to address these failures require policy coherence at national and international levels. This section proposes actions to address these systemic issues, fostering coherence at national, European, and international levels.

Measures at national level

The prioritization of advanced therapies as a health and industrial objective in Spain has shown promising results, creating an ecosystem that can successfully combine accessibility and innovation. However, this ecosystem remains solely focused on providing access nationally and does not direct its actions toward fulfilling the Human Right to health and improving equitable access to medicines beyond national borders. Therefore, we call on the Government:

- In line with World Health Assembly Resolution 72.8, supported by Spain in 2019, to publish net price information, as well as the the processes for determining them.
- Similarly, to improve transparency regarding the production and development costs of publicly funded and developed advanced therapies, as well as their prices in the countries where they are marketed.
- To broaden the objectives of accessibility and affordability for publicly funded and developed advanced therapies beyond the NHS, ensuring global accessibility. To achieve this, the Government should collaborate with public and private organizations financing the development of these therapies and those organizations marketing them, to develop global access plans that include but are not limited to non-exclusive licenses, technology and knowledge transfer, academic collaboration, or funding clinical trials in multiple countries.

European-Level Measures

At the European level, incentives aimed at fostering the development of orphan drugs must be reformed to ensure greater transparency and equity. As this document has shown, the misuse of orphan drug incentives hinders equitable access and affordability and may obstruct the development of public therapies like ARI-0001. Therefore, we urge the Government:

- To oppose the extension of Market Exclusivity periods, particularly when orphan drugs demonstrate sufficient economic profitability.

- To propose a comprehensive definition of orphan drugs, based not only on disease prevalence but also on a clear justification that without the incentives provided by legislation, the investment in R&D would not be economically viable.
- To introduce criteria for social return to access incentive packages, such as the requirement of publishing development and production costs, net prices, public, philanthropic, and private funding received during product development, or preparing a global access plan.
- To waive regulatory fees for academic and non-profit entities developing orphan drugs.
- To protect the Hospital Exemption clause based on the interpretation applied in Spain.
- To promote Transparency across Member States, collaborating to share information on net medicine prices to obtain data that can lead to lower prices.

Equity and Transparency in the Rare Diseases Resolution

All these recommendations for national and European actions must be reflected in Spain's proposals to promote equity and global access in the Rare Diseases Resolution. To this end, we suggest the following areas to be included in the Resolution text:

- Definition of Rare Diseases: The definition should account for both prevalence and economic viability.

  "Calls upon Member States to collaborate with the World Health Organization to develop a comprehensive and harmonized definition of rare diseases that considers not only the low prevalence of such conditions but also the lack of economic viability for the development of health products addressing them as fundamental criteria for receiving public incentives."

- Conditionality and Prioritization of R&D: Given the public and philanthropic funding invested in R&D for rare diseases, provisions must be included in funding agreements to promote equitable global access. Existing incentives should also be linked to global access plans.

  "Recognizing that public and philanthropic investments in research and development for rare diseases must ensure that resulting health products are accessible and affordable globally, particularly in resource-limited settings, and that such agreements promote transparency, equity, and sustainability."

  "Urges Member States to include provisions in publicly and philanthropically funded research agreements for rare diseases that promote equitable global access, including, but not limited to, conditions related to non-exclusive licensing, affordable pricing strategies, and the transfer of technology and knowledge."

"Link national and regional incentives for rare disease therapies to commitments for equitable access, including transparent pricing strategies, global access plans, and measures to ensure affordability and sustainability."

"Prioritizes research and development efforts that address the unmet needs of people living with rare diseases, including through international collaborations, equitable funding mechanisms, and sustainable production and distribution models."

- Regulatory Procedures: Disseminating successful examples, such as Spain's interpretation of the hospital exemption, could lead to similar procedures being adopted in other regions.

  "Calls upon Member States, with the support of the WHO, to work towards the harmonization of regulatory procedures for the evaluation and approval of safe, effective, and high-quality therapies for rare diseases, including specific frameworks for advanced therapies, particularly those governing non-routine and individualized use of these therapies."

- Transparency: In alignment with prior World Health Assembly resolutions, Member States must enhance transparency in the pharmaceutical sector, particularly concerning rare diseases.

  "Recognizing that the lack of transparency in prices and costs, along with the absence of open data on research costs and outcomes, hinders equitable access to rare disease therapies, disproportionately affecting low- and middle-income countries."

  "Urges Member States to take appropriate measures to implement the mandate established in World Health Assembly Resolution 72.8 on 'Improving the Transparency of Mark ets for Medicines, Vaccines, and Other Health Products'."

- Knowledge and Technology Transfer: building on lessons learned from the COVI D-19 pandemic, knowledge and technology transfer are essential to improving global equitable access.

  "Recognizing that equitable access to therapies for rare diseases, especially advanced therapies, depends on strengthening global capacities for research, development, and production, including the transfer of technology and knowledge, particularly benefiting low- and middle-income countries, through collaboration and international support."

  "Fosters global knowledge-sharing and technology transfer, coordinated by the WHO or relevant mechanisms, to facilitate the production and equitable distribution of rare disease therapies."

- Use of TRIPS Flexibilities: explicit recognition of countries' rights to use TRIPS flexibilities can improve access to generic medicines, avoiding external pressure from other parties.

  "Reaffirms the right of Member States to use the flexibilities provided under the TRIPS Agreement and the Doha Declaration to ensure access to affordable health products for rare diseases and encourages collaborative efforts to maximize the use of these flexibilities where necessary."

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Methodological Note

For the analysis of market exclusivity for CAR-T therapies in Europe, 10 years were added to the orphan drug designation date whenever this date was after the marketing authorization date. In cases where the designation date preceded the marketing authorization date, 10 years were added to the latter.

For the analysis of clinical trials, all non-observational studies listed on www.clinicaltrials.gov resulting from a search for the commercial names of the treatments mentioned above were selected.

You can access the databases here: File.