EXECUTIVE SUMMARY

Annual Report on ACCESS 2022

of Orphan Drugs in Spain

aeLmhu

INDEX

01 AELMHU ACCESS REPORT

The Spanish Association of Orphan and Ultra Orphan Drug Laboratories (AELMHU) publishes the main conclusions of its Annual Report on Access to Orphan Medicinal Products (ODs) in Spain.

This document analyses the status of products with trade name and positive orphan designation by the European Medicines Agency (EMA) as of 31th of December 2022, as well as the procedure followed by these products when they arrive in our country, from the assignment of the National Code (NC) by the Spanish Agency for Medicines and Health Products (AEMPS), to their public funding.

For more than a decade, AELMHU has been working to offer more and better indicators that allow all those interested -patients, scientific community, professionals, industry, public decision-makers and society - to periodically evaluate the availability of innovation in a field as complex and, at the same time, as hopeful as rare diseases.

For our Association it is an honour and a responsibility to know that today our reports already represent the main reference of data on access to orphan and ultra-orphan drugs in Spain. That is why, as a novelty this year, we wanted to do two things: first, to go deeper into the analysis of some relevant aspects, such as those orphan treatments that have community marketing authorisation but do not yet have a National Code in our country, analysing the deadlines and the therapeutic areas to which they correspond. And secondly, to put forward a set of proposals to improve the situation of orphan products in Spain.

AELMHU's mission is to contribute to improve the situation of people affected by rare or infrequent diseases, promoting knowledge of their pathologies and recognition of the therapeutic and social value that orphan drugs have in their daily lives and those of their families.

For this reason, after such atypical years led by the Covid19 pandemic, and at the beginning of a decisive course for our industry -in which the approval of the new Law on Guarantees and Rational Use of Medicines, the new European Regulation of ODs, the new Pharmaceutical Strategy for Europe or the Strategic Plan for the Pharmaceutical Industry 2023-2025, as well as the Spanish presidency of the Council of the EU- AELMHU wants to continue projecting more and better indicators to contribute to the common objective of streamlining the availability of pharmaceutical innovation in Spain.

AELMHU is a non-profit organization that, for more than a decade, has brought together pharmaceutical and biotechnology companies with a strong commitment to discover, research, develop and commercialize innovative therapies capable of improving the situation of patients suffering from these so-called rare pathologies.

The current members of AELMHU are **Alexion AstraZeneca Rare Diseases, Alnylam, AMRYT Pharma, Biocryst, Biomarin, Chiesi, CSL Behring, Ferrer, Gensight Biologics, Insmed, Ipsen, Jazz Pharmaceuticals, Kyowa Kirin, Novartis Gene Therapies, PTC Therapeutics, Sanofi, SOBI, Takeda, UCB, Ultragenyx and Vertex**.

02 REPORT METHODOLOGY

This executive summary of the Report on Access to Orphan Drugs (ODs) in Spain 2022 has been prepared by Lasker on the basis of the information identified by Bioinnova Consulting at the request of AELMHU, through a data review methodology focused on four phases:

01 Identification of drugs with orphan designation

The active substances with orphan designation (OD) in force as of 31 December 2022 (more than 1,800) have been identified among the more than 2,000 active substances with orphan designation given by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). The OD is granted during the early stages of a medicine's research, so that among the active ingredients with a current OD, those with a trade name (more than 200) are identified in each report and, of these, duplicates are eliminated because they have several indications. Eliminating these duplicities, we find **195 medicines** with **OD** in force until 31 December 2022 and with a trade name.

02 Drugs withdrawn

Next, an analysis was made to know how many of these ODs have been withdrawn (or have not yet been included) in the European Commission's Community Register of Orphan Medicinal Products for marketing in the European Union (n=49). The result is the **number of ODs with marketing authorisation (MA)** as of 31 December 2022, in European countries for marketing **(n=146)**.

03 Drugs with National Code

The third step has been to identify which of those marketing-approved brand-name medicines, which are approved for marketing in the European Union, have a **National Code (NC)** from the AEMPS for marketing in Spain **(n=123)**.

04 Funded drugs

Lastly, they identified which and since when the ODs **were funded** by the **NHS** according to the information contained in the Nomenclátor of the Ministry of Health **(n=63)**. The date of funding was taken as the first date of discharge.

Note: Due to the fact that data cannot be obtained from any public source, this document does not reflect those medicines that are available in our country under specific situations and special authorisations within the framework of Royal Decree 1015/2009 (compassionate use, use under conditions other than those authorised or access to foreign medicines).

03 CURRENT CONTEXT OF ORPHAN DRUGS

ODs are innovative treatments, many of them of biotechnological origin, aimed at establishing a diagnosis, preventing or treating rare or infrequent diseases (RRDs) that affect fewer than 5 out of every 10,000 people and have no alternative treatment.

It is estimated that there are between 6,000 and 8,000 RRDs in the world, of which only 5% have some kind of diagnostic tool or treatment. Research and innovation in this field represent an urgent need for society as a whole.

Aware of this situation, in the year 2000 the European Parliament and the Council of the EU approved EU Regulation 141/2000, which will soon be updated, this regulation established that **"patients affected by rare diseases should be entitled to the same quality of treatment as other patients"**, incorporating incentives to improve knowledge and promote research, development and commercialization of drugs in the field of RRDs.

Since then, the legislation promoted by the EU and Spain **has made unquestionable progress**. In fact, especially in recent years, **the research efforts of pharmaceutical laboratories have been strengthened and the willingness of a growing number of companies capable of providing innovations in this field has increased**.

This is reflected in the data from the latest Annual Report on Clinical Trials in Rare Diseases in Spain, prepared by AELMHU, according to which **Spain reached a record number in 2021 with the launch of 225 trials for the research of rare diseases**, 23% of the total number of trials initiated in our country, which represents 3 points more than in 2020.

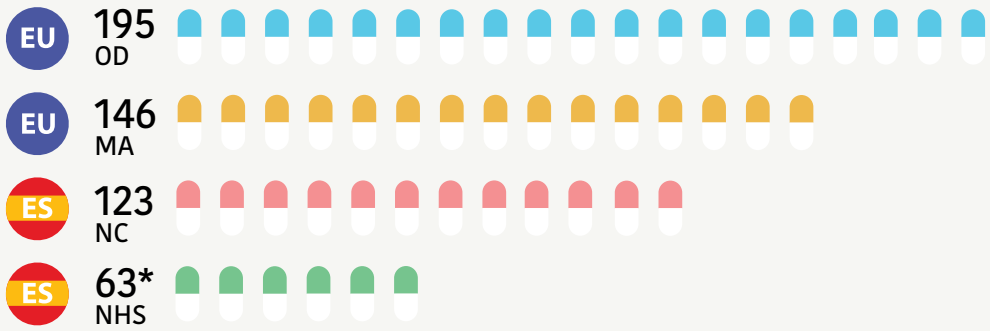
However, **this interest of the industry to delve into such a complex field as the rare diseases is not having a direct reflection in the availability for Spanish patients**, as reflected in this report.

In this sense, AELMHU´s will is to deep in numerous aspects such as **equity in access** to these treatments **or the streamlining of bureaucratic processes** to facilitate effective access to a unique opportunity for many people suffering from these types of pathologies who have not found a therapeutic alternative.

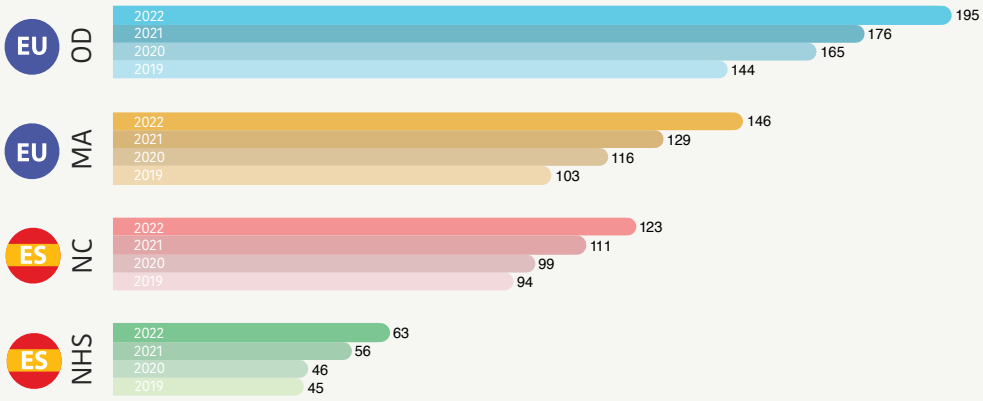
04 ORPHAN DRUGS IN THE EU AND SPAIN

The year 2022 closed with **195 drugs with positive orphan designation** in the EU, 146 of which **have EU marketing authorisation, 123** obtained the **National Code** in Spain (84%) and **63** are funded by the National Health System (43%).

Main EU and Spanish indicators



Evolution of EU and Spanish indicators (2019 - 2022)



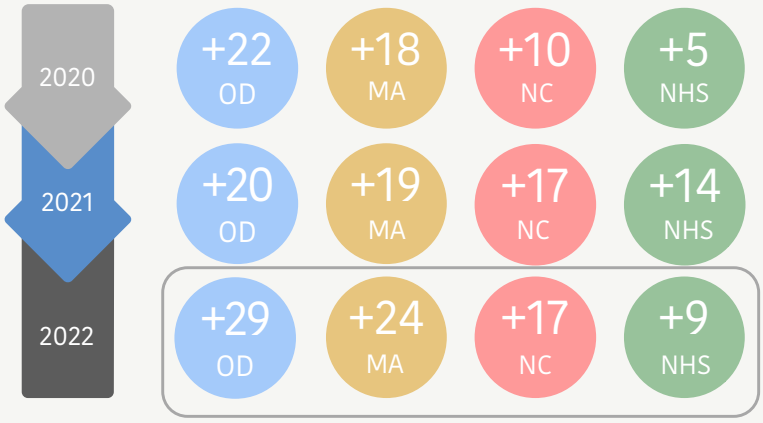
Once again, ODs in the EU and Spain improved in all indicators:

- 11% more positive EMA orphan designations, to 195 products, up from 176 in 2021.
- 13% more EU marketing authorisations, from 129 in 2021 to 146 in 2022.
- 11% more ODs obtaining National Code in our country, from 111 in 2021 to the current 123.
- And 12.5% more orphan products funded, up to 63 ODs funded, 7 more than in 2021.

* Throughout the report, Onivyde® is cluded in the count of medicines funded by the NHS as of 31/12/2022, as Onivyde® has been registered in the Nomeclátor during December 2022. Despite its positive funding agreement in 2018, in 2019 the company decided to exclude the drug from NHS provision, which is why it was not counted among the products funded and available within the NHS presented in previous reports. For more information on Onivyde®: Here.

Summary of the evolution of new ODs 2020 - 2022

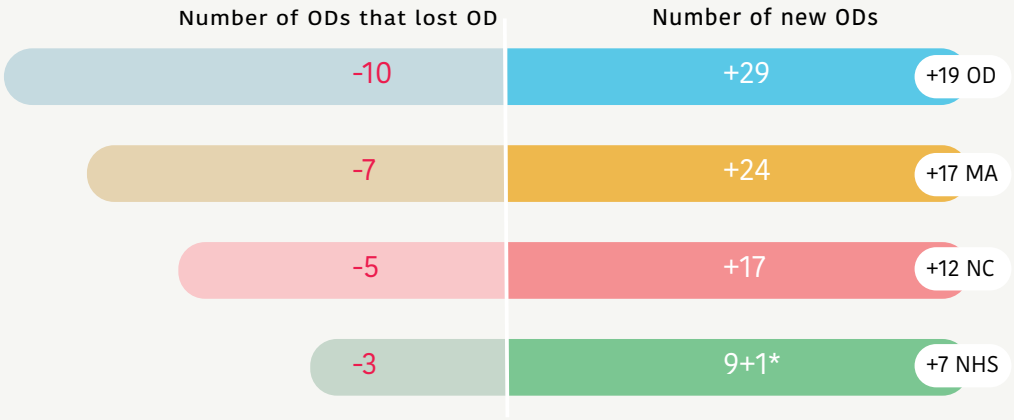
When we analyse the overall annual variation, the following graph shows that in the 2020-2022 period while very positive figures are achieved in all community parameters at national level the indicators remain stagnant or even worsen.



According to the chart above, in 2022:

- **A maximum of positive orphan designations** was reached, with 29 total new designations, 9 more than in 2021.
- There were, also, **a maximum of 24 marketing authorisations**, 5 more than the best year, 2021, when 19 new community authorisations were reached.
- **The number of new National Codes remained** the same as in 2021, with 17 new NCs.
- **And the number of new drugs funded fell** by 36%, from 14 in 2021 to 9 in 2022.

Variation of indicators between 2021 and 2022



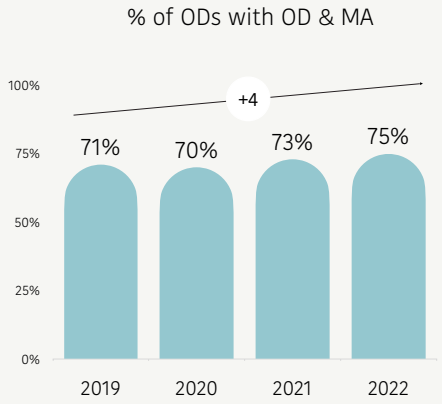
In relative terms, weighting expired or withdrawn orphan designations and marketing authorisations, National Codes or funding that have been revoked, etc., the main figures for 2022 are as follows:

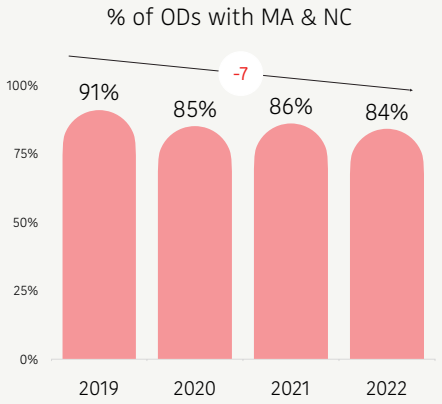
- There were 29 new orphan designations and 10 drugs lost this status, resulting in a net increase of **19 new positive designations.**
- There were 24 community marketing authorisations granted, and 7 ODs lost orphan designation, putting us at **17 net new MAs.**
- 17 new ODs obtained NCs in Spain but, at the same time, 5 lost orphan designation, so there is a net increase of **12 new NCs.**
- 9 ODs were approved for funding and 1 product was reinstated in the Nomenclator, while 3 ODs lost orphan designation, **bringing the number of new drugs funded to 7.**

Comparison between indicators: 2019 – 2022

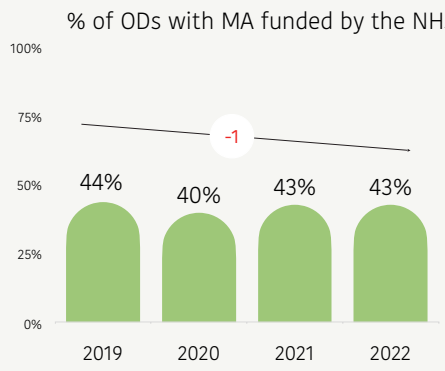
As the following graph reflects, of the 100% of ODs with positive OD, 75% **have community marketing authorisation, representing a 2% increase** over the 2021 figures.

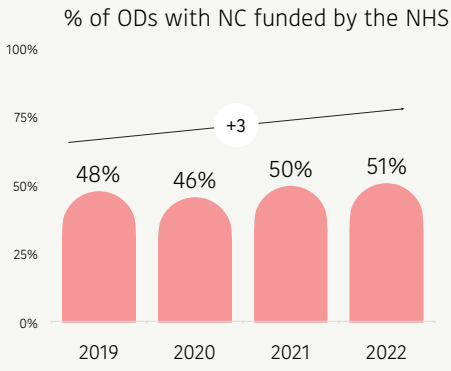
In addition, **the proportion of National Code applications in Spain decreases for the fourth consecutive year,** from 91% of the total in 2019 to 84% in 2022, down 7 points.





43% of them are funded in our country, identical percentage to the previous year, while **the percentage of ODs with NC that are funded by the NHS remains stable, with a slight growth from 50% in 2020 to 51% in 2021.**

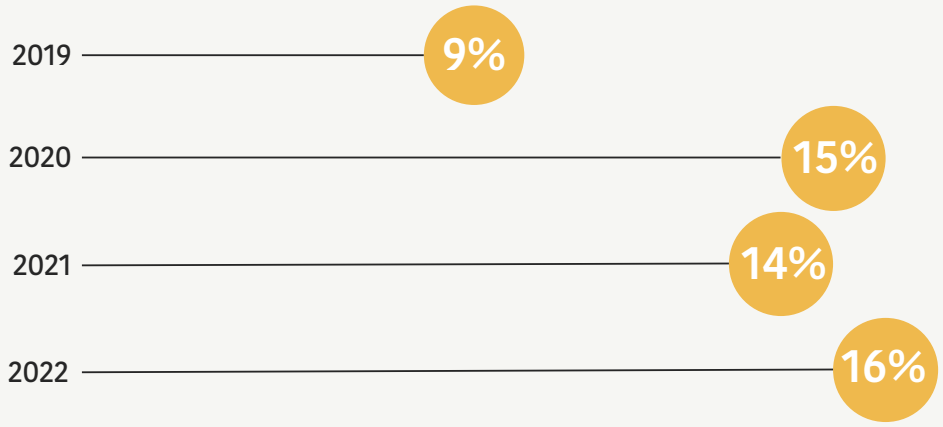




05 ORPHAN DRUGS WITH MARKETING AUTHORISATION WITHOUT NATIONAL CODE IN SPAIN

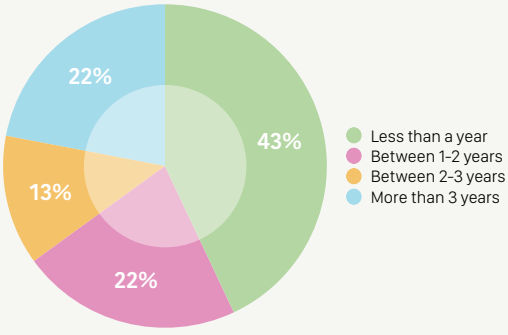
As of December 31 of 2022, there were 23 ODs with MA that had not yet arrived in Spain (without NC), which represents **16% of the ODs authorised at the EU level, the highest figure in the last four years**.

% Orphan drugs with MA without NC (2019-2022)

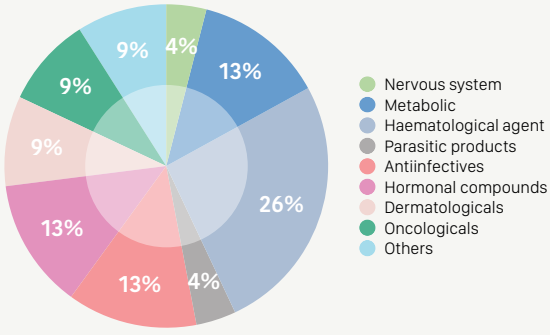


57% of them received their marketing authorisation in the EU more than a year ago, with **hematological agent** (26%), **metabolic** (13%), **hormonal compounds** (13%) and **antiinfectives** (13%) agents predominating by therapeutic area. In addition, **3 of them are advanced therapies**.

Waiting years



Therapeutic area



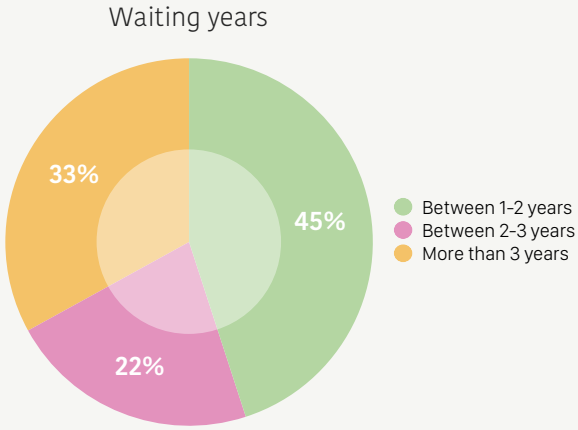
06 ORPHAN DRUGS FUNDED IN SPAIN DURING 2022

In 2022, 9 new ODs were funded in Spain: 2 in the first four-months period, 4 in the second four-months period of 2022 and 3 in the third four-months period.

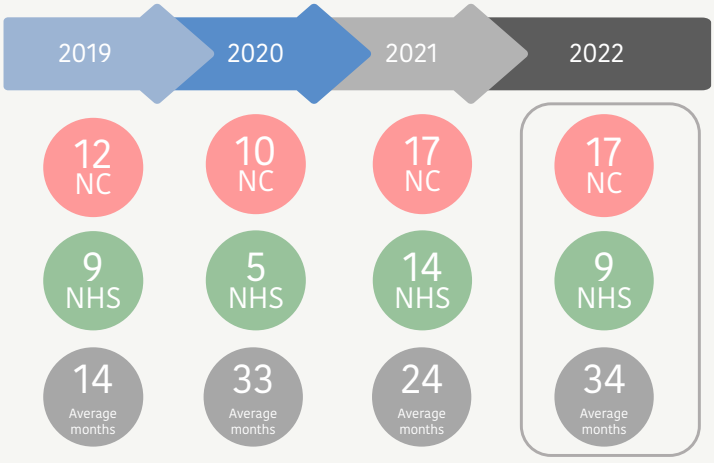
The average time elapsed between the community marketing authorisation of the 9 new products funded and obtaining the National Code was 8 months, while the waiting period from the NC to obtaining the positive price and reimbursement decision exceeded 34 months, 10 more than in 2021 (+42%), the worst record in the 2019-2022 series.

In addition to the 9 new products funded throughout 2022, 100% have taken at least one year to obtain pricing and funding; 43% waited between one and two years; and 55% two years or more.

Percentage of products funded in 2022 by waiting years



Evolution of new ODs in Spain and of average waiting time for funding* 2019 – 2022



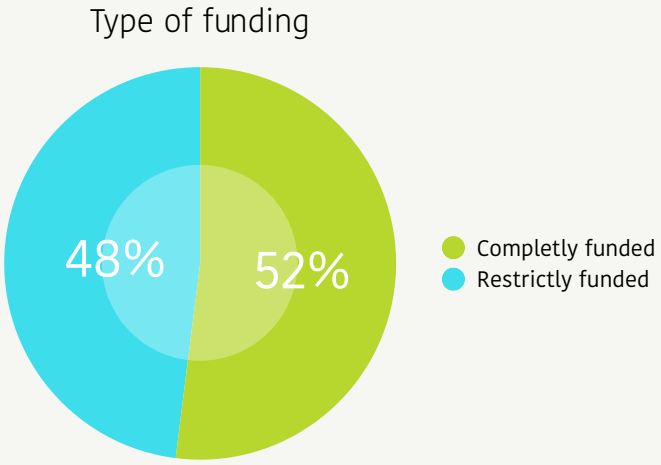
*Average waiting time between date of NC and funding date.

On the other hand, **60% of the 9 new products funded during 2022 have restricted funding** (based on EMA-approved indications) and **100% of them have conditional funding.**

In addition, **56% of them have 2 or more funding conditions, all of them have follow-up conditions,** 44% (4 of 9) are subject to maximum cost per patient and 22% of the have a expenditure ceiling.

In total, **63 ODs** are funded in Spain, which represents 51% of the total number of ODs with NC in Spain, and 43% of those with MA at the European level.

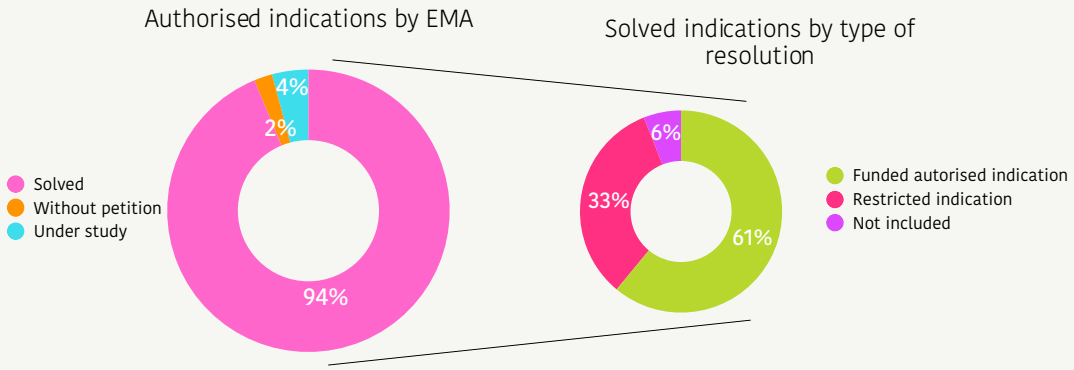
Detail criteria and conditions of the ODs funded by the NHS during 2022



Out of these, as the above graph indicates, 48% (30) of the 63 ODs that currently have a positive price and reimbursement resolution in the NHS are **funded with restrictions**, either due to restrictions in the authorised indication(s), or because they have an unfunded indication.

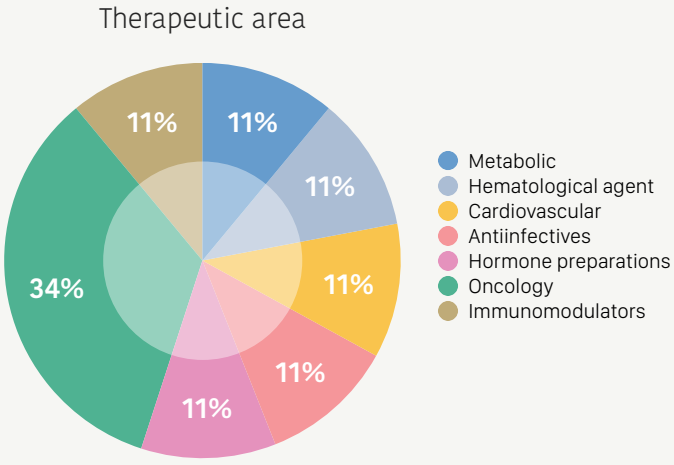
The **63 ODs** have a total of **99 indications authorised by the EMA, and, of these, 57 are funded without any restrictions**, as detailed in the following image:

Status of authorised indications of funded ODs



Out of the 9 new ODs funded this year, 34% are indicated for oncological diseases, and 66% for metabolic, hematological agent, cardiovascular, anti-infectives and hormone preparations, among others.

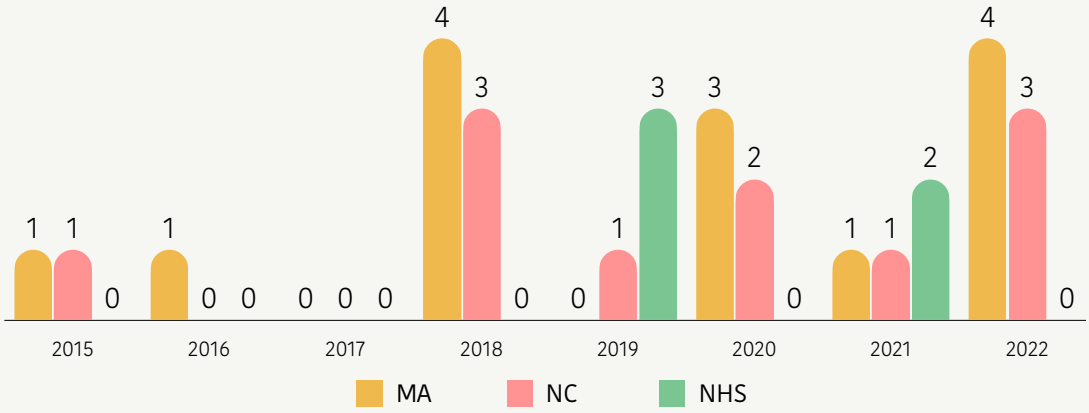
Percentage of products funded in 2022 by therapeutic area



07 ADVANCED THERAPIES WITH ORPHAN DESIGNATION

During 2022, **4 therapies have been authorised in Europe, 3 have obtained NC, but none have been funded by the NHS**.

Currently, 14 advanced therapies with orphan designation have marketing authorisation in the EU, 79% (11) have National Code, 12% more than in 2021, while only 36% (5) are funded by the NHS, a decrease in the ratio of funded therapies of 6% compared to last year.

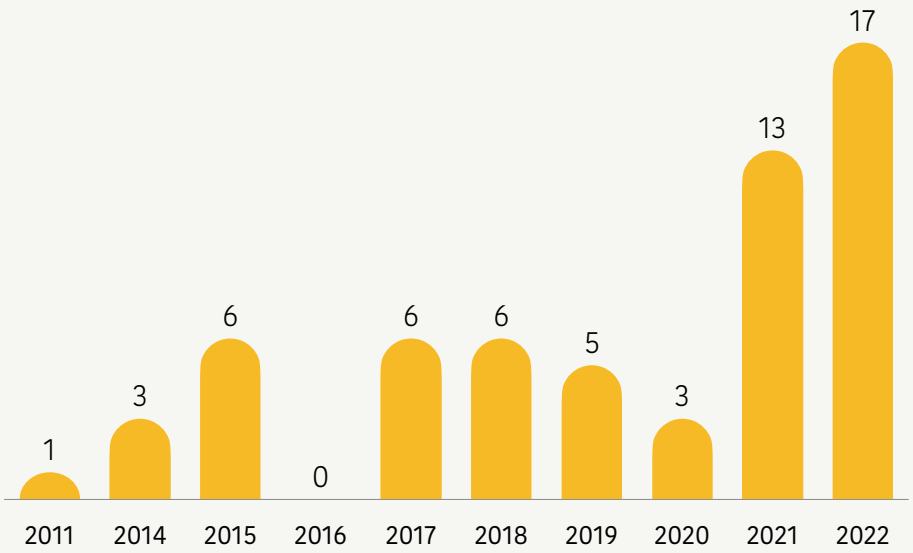


08 ORPHAN DRUGS UNFUNDED

There are currently **60 unfunded orphan drugs in Spain, 5 more than in 2021.**

Of these, 53% (32) have received a negative funding resolution while the remaining 47% (28) are either under study or have not yet applied for funding.

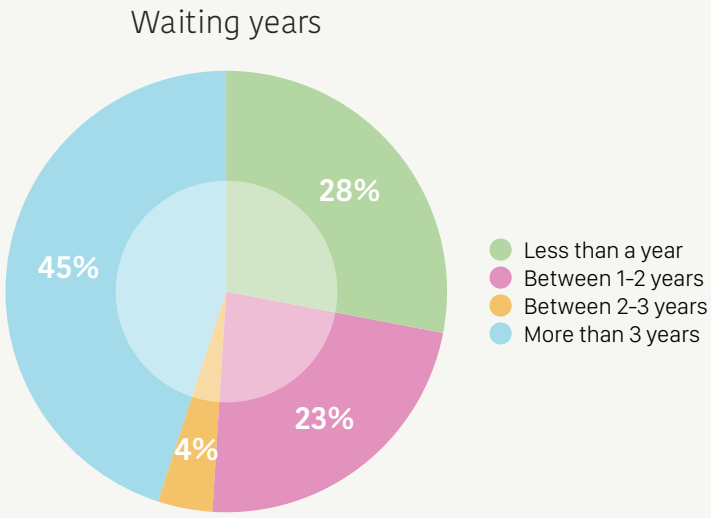
Number of not funded orphan drugs in Spain by year of NC



As reflected in the graph above:

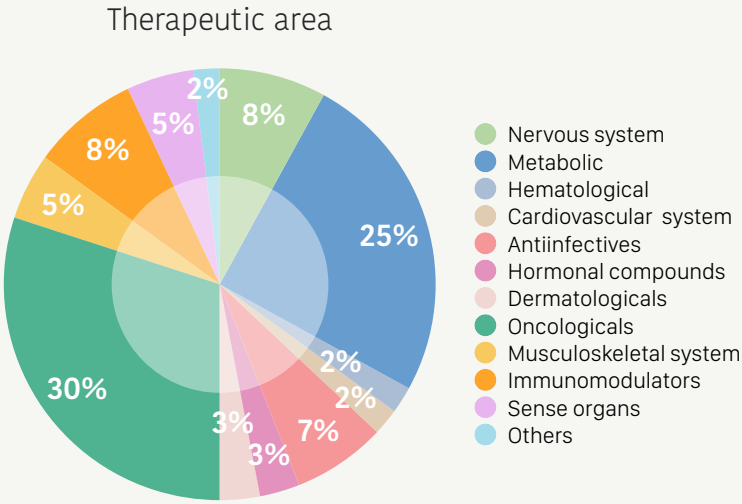
- **El 17%** (10 ODs) have been awaiting public funding since 2011-2015.
- **El 55%** (33 ODs) with NC in the 2017-2021 period remain unfunded by the NHS.
- **El 28%** (17 ODs) received NC in 2022.

ODs. unfunded by years of waiting



In addition, **nearly half (45%) of the ODs with unfunded NC have been waiting more than 3 years for incorporation into the NHS**, while only 28% have been in this situation for less than one year.

ODs Unfunded by therapeutic area



Of the unfunded ODs, 30% are for oncological diseases, 25% for metabolic diseases and 8% for immunomodulators, among others.

09 MAIN CONCLUSIONS OF THE REPORT

01 **In ALMHU´s view, the access data for ODs in 2022 reflect that the future of orphan therapies in the EU is increasingly positive**, which represents extraordinary news for all those patients and families who have not yet found a diagnosis or treatment for their pathologies and look to pharmaceutical innovation with great hope.

02 In the last year, **all EU parameters have improved**, with record highs in both new orphan designations (29) and marketing authorisations (24), which has raised the number of products with positive orphan designation to 195 and with marketing authorisation to 146.

03 On the other hand, **the figures for Spain are not so positive**: the percentage of National Code applications with respect to the total number of ODs authorised at the European level is decreasing, **the number of new ODs funded regarding 2021 is decreasing and, above all, the waiting time to reach a positive price and reimbursement resolution in the NHS is becoming an increasing concern.**

04 **In terms of funding, the percentage of ODs funded by the NHS with respect to the total number of European authorisations remains stable at 43%**: Spain finances 4 out of every 10 ODs approved by the EU. However, while in 2021 14 new products were approved for funding, in 2022 only 9 new ODs have been funded, which represents a notable decrease in positive pricing decisions.

05 Furthermore, **60% of the 9 new products funded during 2022 have restricted funding** (based on the indications approved by EMA) and **100% of them have conditional funding: 56% of them are subject to 2 or more funding conditions, all have monitoring conditions**, 44% (4 of 9) are subject to maximum cost per patient and 22% (2) to a spending ceiling.

06 Meanwhile, as of December 31, 2022, **there were 23 ODs approved at the European level that did not have a NC in Spain**, 16% of the total number of those authorised in the EU, the highest figure in the last 4 years. Of these, 57% have been authorised for more than a year but have not yet entered our market, which shows a **lower availability of relevant innovations for Spanish patients.**

07 Likewise, even though these developments are the future of healthcare, particularly in the field of RR, **in 2022 Spain has not funded any advanced therapy with orphan designation**. And of the 14 therapies with marketing authorisation in the EU, 79% (11) have a National Code, 12% more than in 2021, but only 36% (5) are funded by the NHS, down 6% from last year.

08 It seems that one of the elements that most influences this situation is the **expandened waiting times, which, far from improving, increased by 42% in the last fiscal year.** As of today, the average time between the NC and the funding of an orphan product **in Spain exceeds 34 months, almost 3 years**, far from the desirable 6 months as the maximum average time for approval and funding.

09 At present, **60 orphan drugs are not yet funded in our country, 5 more than in 2021, of which nearly half (45%) have been waiting more than 3 years** for their incorporation into the NHS.

10 AELMHU ASSESSMENT AND RECOMMENDATIONS

01 The access data for ODs for the year 2022 lead us to demand, once again, that **Spain should be able to speed up the approval processes for ODs**, especially since their efficacy has already been accredited by the European Medicines Agency (EMA).

02 AELMHU has been defending for many years the **health value, but also the economic and social value provided by orphan treatments for patients with RRDs, based on the conviction that innovation is a tangible asset for society as a whole and a project for the future and for the country.**

03 In this sense, having overcome the worst of the health crisis caused by Covid19 , and in such an important year for Spain, **the acceleration in the research and development of new orphan drugs represents a great opportunity** that should stimulate the sum of efforts to place us at the forefront in terms of efficiency, responsiveness and attractiveness.

04 **It is necessary to continue advancing in many aspects** such as the recognition of the economic and social value of pharmaceutical research on new products and indications, equity in access to these treatments, streamlining bureaucratic processes, improving the evaluation process, etc., and providing greater certainty, transparency and participation throughout the approval process, among other issues.

05 **AELMHU would like to reiterate its invitation to everyone** -industry, patients, scientific community, professionals and public decision-makers- **to join forces in order to find solutions that improve the quality of life of all those who suffer from a minority disease**.

06 For this reason, and as we have proposed to the Ministry of Health in a document of recommendations with the occasion of the Preliminary Public Consultation on the Draft Bill amending the Consolidated Text of the Law on Guarantees and Rational Use of Drugs and Medical Devices, we wish to make a **series of proposals** in the following areas:

- **Funding and pricing of ODs and their inclusion in the pharmaceutical provision of the NHS,** to provide certainty, agility and greater transparency in the processes.
- **Evaluation of the drugs,** to favour consensual solutions that allow information to be shared in an agile manner, establish a predictable procedure for the presentation, resolution and reporting of allegations and **increase patient and clinician participation.**
- **Funding linked to clinical and financial results,** stimulating greater transparency and governance, allowing for homogenization of the existing territorial disparity, and facilitating data collection.
- **Reference Price System,** through the exclusion of ODs.
- **Streamlining access,** with new mechanisms that reflect the specificities of rare diseases and orphan drugs, as well as the need to incentivize them, in line with the provisions of the European regulation on orphan drugs.
- **Incorporation of the lessons learned from the pandemic,** in terms of streamlining authorisation and marketing processes, use of digital solutions for clinical trials, regulatory submissions, home care and public-private collaboration.

- **Adequate funding** for the Spanish Agency for Medicines and Health Products (AEMPS) so that it can carry out its work with agility and guarantees.
- **Ensuring equity in access between different Autonomous Communities.**
- **Incentives for pharmaceutical innovation and support for the digital transformation of the sector.**

11 BIBLIOGRAPHY

01 Drugs with positive orphan designation from the European Medicines Agency

02 Community Register of Orphan Drugs

03 Orphan Drugs authorized by the AEMPS

04 Orphan Drugs funded by the NHS (Nomenclator)

05 Agreements of the Interministerial Commission on Drug Prices

12 ACRONYMS

MA: European Marketing Authorisation by centralized procedure

AEMPS: Spanish Agency for Medicines and Health Products

CHMP: Committee for Medicinal Products for Human Use

NC: National Code

COMP: Committee for Orphan Medicinal Products and Medicinal Products

CIPM: Interministerial Commission on Drug Pricing

RRDs: Rare Diseases

EMA: European Medicines Agency

ODs: Orphan drugs

OD: Orphan Designation

NHS: National Health System

EU: European Union

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