# Annual ObserveMHe Report

ObserveMHe
OBSERVATORIO DE
MEDICAMENTOS HUÉRFANOS

## Orphan Drugs approved by the European Commission and authorized in Spain

# Introduction

The current ObserveMHe 2021 annual report it is born as a continuity of a research project developed by Omakase Consulting. The report covers the 2003-2021 period and includes orphan drugs approved by the EMA that asked marketing authorization in Spain; and has been sponsored in collaboration with Pfizer and Ipsen pharmaceutical industries.

The report's content and purpose highlight the need to understand the pricing and market access situation of orphan drugs in Spain and its evolution over time. From its evolution we can do the methodological exercise to identify both the variables from the disease to the regulatory process, that might be associated to pricing and reimbursement decision making and process of orphan drugs in Spain.

From its relevant analysis by different agents, i.e.: health administration; health professionals; patients and industry, it is reasonable to think that an appropriate reflection could be conducted to assess the results of the current model; as well as to identify the advantages and deficiencies observed and to promote proposals for improvement.

With this report, we respectfully aspire to promote a creative framework to improve the market access, in magnitude and speed, to orphan drugs for patients with rare diseases in Spain, always considering the necessary future economic sustainability of our National Health System.

In this context, and in line with the editorial released in this report, on 28 February 2022 we will have the opportunity to provide visibility to this work through the ObserveMHe platform. ObserveMHe is a multidisciplinary platform that will aim to promote information and knowledge on orphan drugs and rare diseases in Spain.

**José Luís Poveda Andrés**

President
AINEERR

# Objectives

01

To describe the Pricing & Reimbursement (P&R) situation in Spain of Orphan drugs (ODs) approved by the European Commission (EC).

To analyse the administrative timelines and the impact of Therapeutic Positioning Report (TPR) on the P&R process of ODs in Spain.

02

03

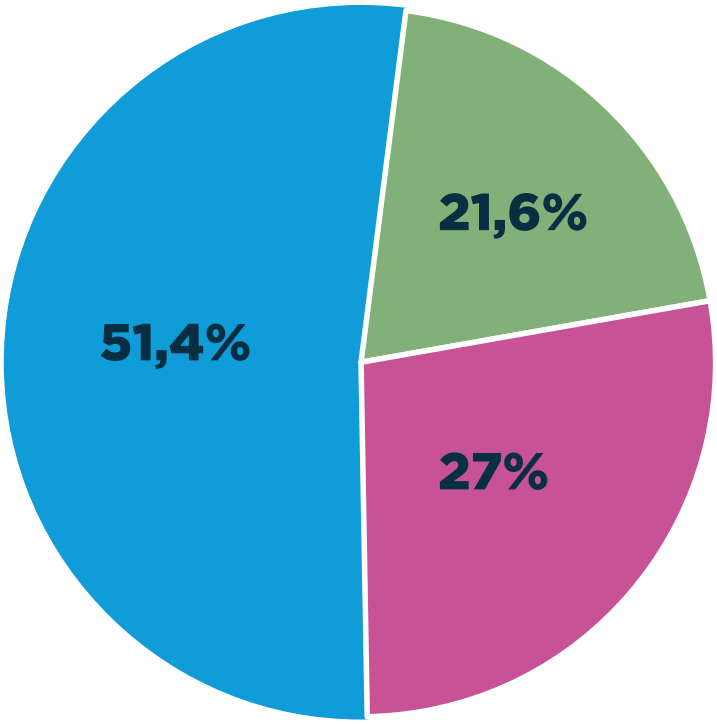
To describe variables that would be relevant for the P&R process of ODs in Spain and establish potential relationships of variables with the reimbursement situation.

# Results

## 01 Description of the Pricing & Reimbursement situation in Spain of Orphan Drugs approved by the European Commission

### Orphan Drugs approved by the European Commission

A total of **128 ODs approved by the European Commission** (EC) were identified, **of which 111 (86,7%) have been granted marketing authorisation in Spain**.




- 57 had **P&R approval**
- 24 were **undergoing the P&R process**
- 30 had **P&R request rejected***

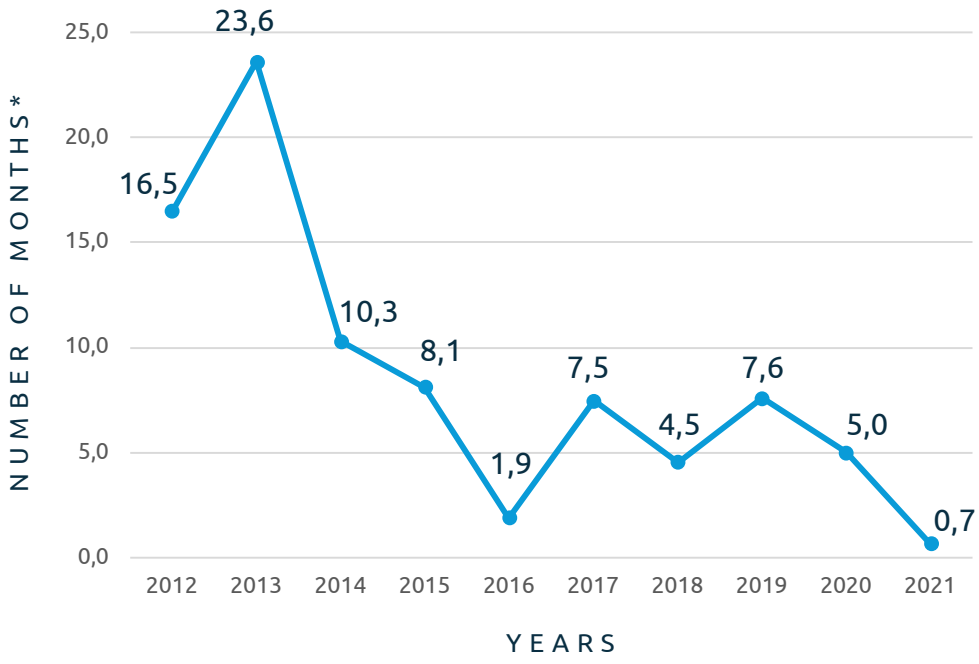
*5 ODs were commercialised in the private market: Bronchitol®, NexoBrid®, Procysbi®, Tobi Podhaler® and Xermelo®.

# 02 Analysis of the administrative timelines and the impact of the Therapeutic Positioning Report (TPR) on the P&R process of ODs in Spain

## 2.1 ANALYSIS OF THE ADMINISTRATIVE TIMELINES OF ODS IN SPAIN

### Approved EC Orphan Drugs with Spanish Marketing Authorisation

The **mean time** from EC approval to Spanish Marketing Authorisation for ODs is shown below:




The **mean time** from EC approval to Spanish Marketing Authorisation for ODs has **shortened over the years**. This would indicate that the European and Spanish agencies have might accelerated the administrative process, or that the Marketing Authorization Holder (MAH) would be asking for P&R in Spain sooner than in the past.

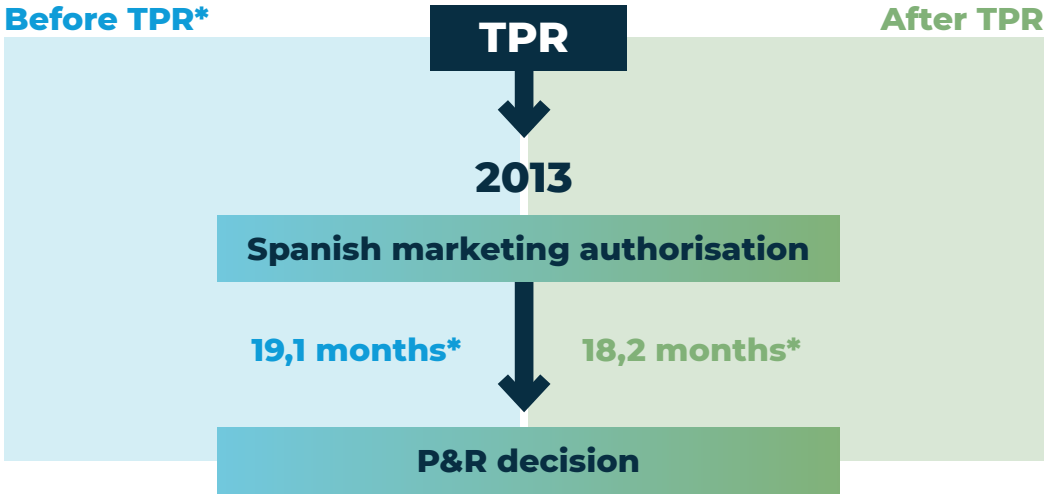
*Mean time

## 2.2 ANALYSIS OF THE IMPACT OF THE TPR ON THE P&R PROCESS OF ODS IN SPAIN

### P&R evaluation timelines have been slightly reduced with the inclusion of TPRs by an average of less than 1 month

In **May 2013, a major change was introduced in the P&R process in Spain: The Therapeutic Positioning Report (TPR)**. The TPR is an evaluation document issued by the Spanish Agency of Medicines and Medical Devices ("AEMPS" from Spanish initials) that aims to determine the adequate positioning relative to what constitutes standard of care for the same indication **to inform P&R decisions in Spain**. The TPR includes a thorough review and summary of relative efficacy and safety data available for the new product.

The mean time of the P&R evaluation process for ODs is shown below, stratified by before (n=15) and after (n=96) the inclusion of the TPR during P&R process in Spain:



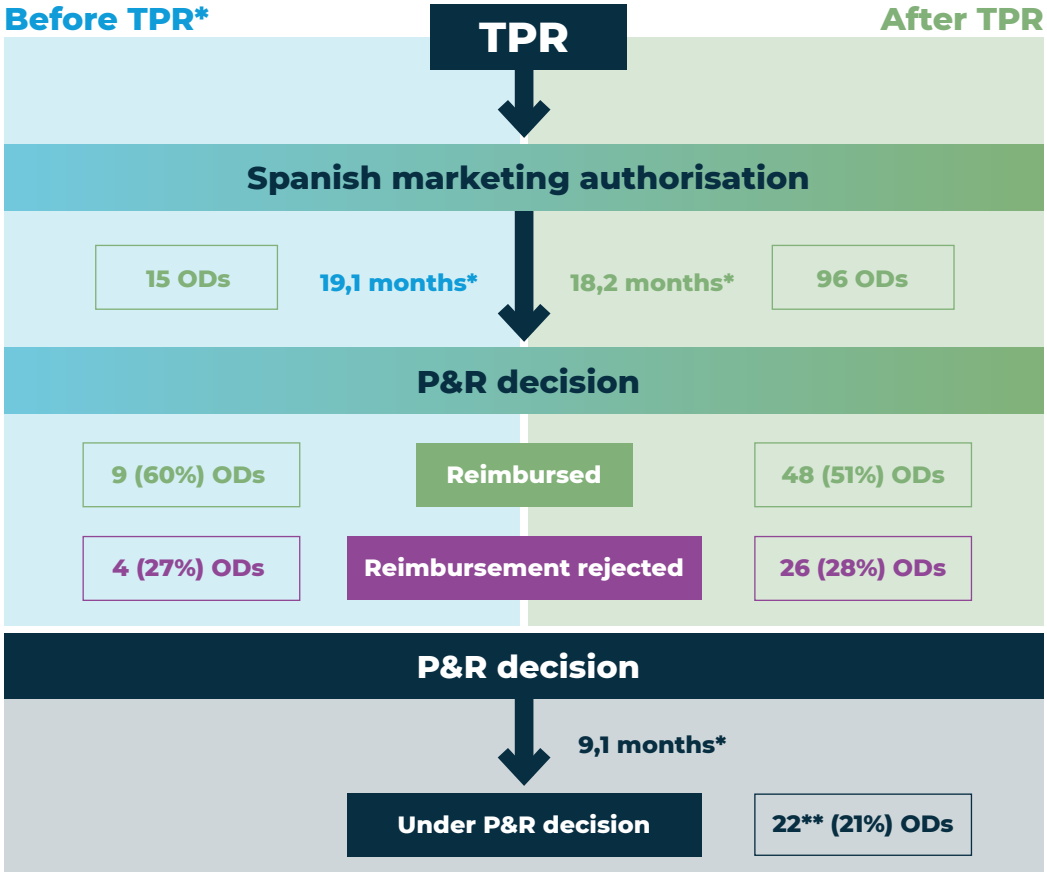

*As the TPR inclusion was gradual, this subgroup includes ODs approved after 2014 that were not assessed with TPR.

1. AEMPS. Propuesta de colaboración para la elaboración de los informes de posicionamiento terapéutico de los medicamentos. 2013. Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/propuesta-colaboracion-informes-posicionamiento-terapeutico.pdf

**Sources:** The EMA's website. www.ema.europa.eu/en; AEMPS. CIMA. cima.aemps.es/cima/publico/home.html; MoH. BIFIMED: www.mscbs.gob.es/profesionales/medicamentos.do

## From all the ODs that have undergone P&R evaluation with the TPR, 51% were reimbursed

**The number (percentage) of P&R approved ODs, the ODs under P&R decision process, and P&R request rejected ODs** after obtaining the **Spanish Marketing Authorisation** are shown below, stratified according to if ODs undergone P&R evaluation with a TPR or not.




*Mean time

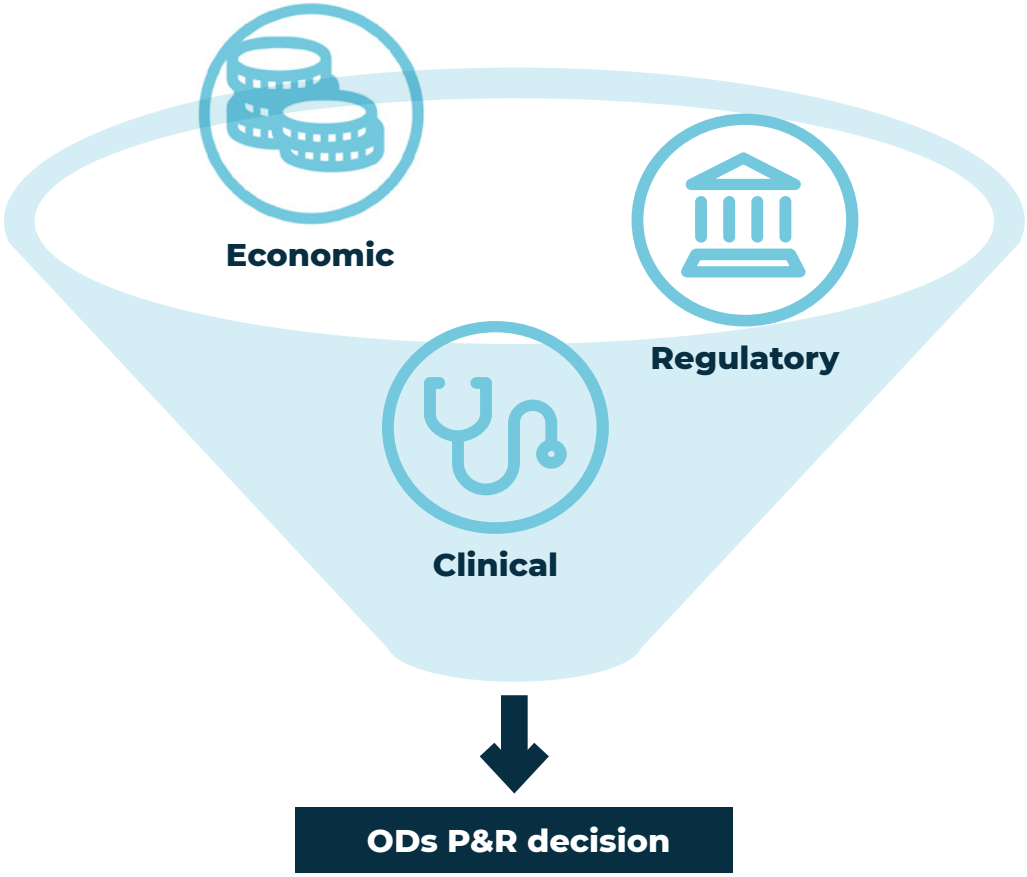
**There are 2 ODs (Xaluprine and Qarziba) without TPR that have Spanish Marketing Authorisation but, with the public available information, it is not possible to know if they are under P&R decision or without reimbursement request, so they have not been included.

# 03 Description of the variables that would be relevant for the P&R process of ODs in Spain and establishment of potential relationships of variables with the reimbursement situation

## 3.1 DESCRIPTION OF THE VARIABLES THAT WOULD BE RELEVANT FOR THE P&R PROCESS OF ODS IN SPAIN

### Clinical and regulatory variables that could be relevant for the P&R process in Spain

In this section, the potential variables that could influence the P&R process in Spain will be described. These are classified into three groups:

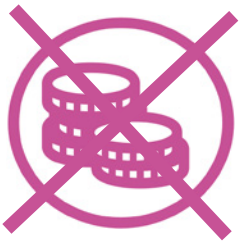


## CLINICAL VARIABLES

Therapeutic area, rarity of disease, existence of therapeutic alternatives, outcomes classification, safety profile and type of population.

## REGULATORY VARIABLES

Conditional approval by the European Medicines Agency (EMA) and Therapeutic Positioning Report (TPR) conclusion in Spain.

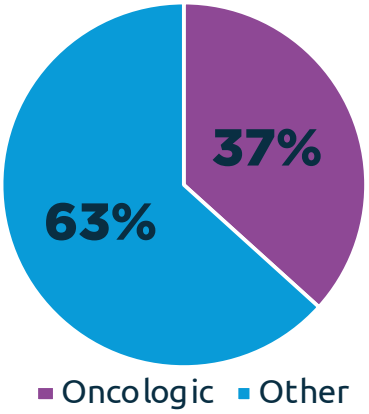


## ECONOMIC VARIABLES were not included in this report because the lack of validity.

Spain operates a dual pricing system for hospital medicines. Official listed prices in the available databases do not reflect reimbursed price agreed with the Ministry of Health. The reimbursed price is usually 40% lower in relationship with the list price.

## Clinical variables

Descriptive results of clinical variables are shown below. Out of the 111 authorised ODs in Spain:

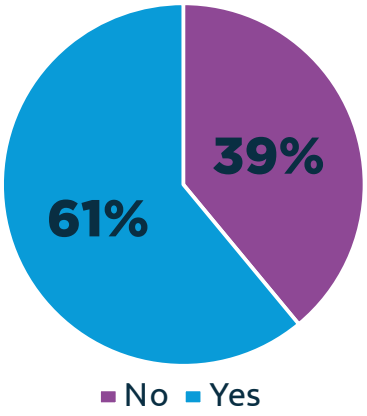


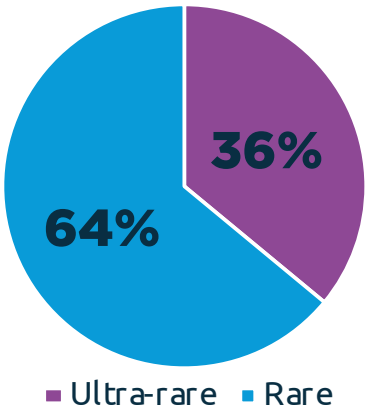
### Therapeutic area

**41 ODs (37%)** were indicated for **oncologic diseases**.

### Existence of therapeutic alternatives

**43 ODs (39%) didn't have any therapeutic alternative indicated** for treating the same indication.



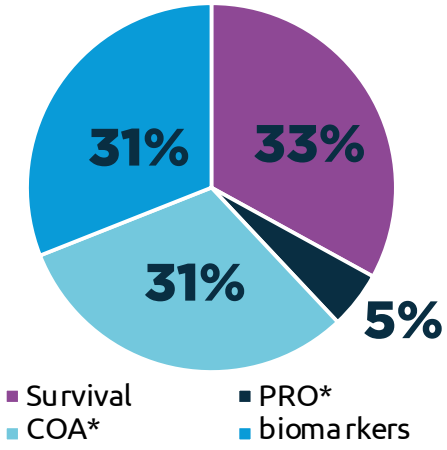



### Rarity of disease

**40 ODs (36%)** were indicated for **ultra-rare diseases** (with a prevalence of <1/50,000 individuals).

## Clinical variables (cont.)

Out of the 111 authorised ODs in Spain :

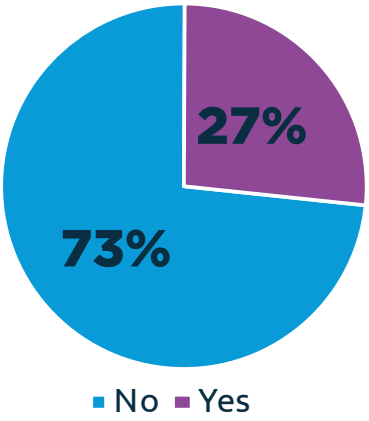


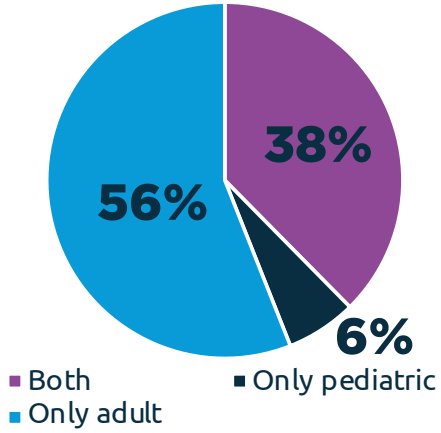

### Outcomes classification

**37 ODs (33%)** have been evaluated with **survival-related outcomes.**

### Saftety profile

**30 ODs (27%) had to conduct a Post-authorisation safety study** (PASS) according to EMA.



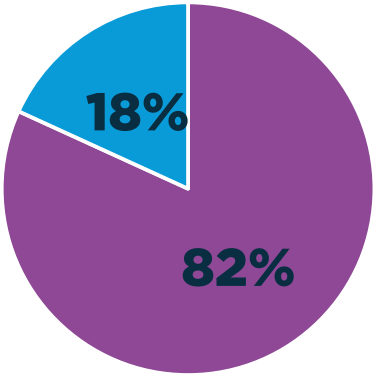

### Type of population

**7 ODs (6%)** were indicated for **paediatric patients only, 62 ODs (56%) for adults only** and **42 ODs (38%)** were indicated **for both** (adults and paediatrics).

*COA: Clinical outcomes assessment, *PRO: Patient-reported outcome

## Regulatory variables

Descriptive results of regulatory variables are shown below. Out of the 111 authorised ODs in Spain:

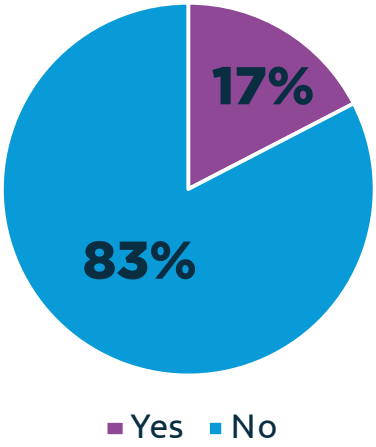



### TPR conclusion*

Out of the 66 published TPR, **54 ODs (82%)** had a **positive conclusion.**

### Conditional approval

**19 ODs (17%) were granted conditional approval** marketing authorisation by the EMA.




* The TPR conclusion refers to the final efficacy and safety conclusion of the ODs according to the TPR. This variable was based on a subjective interpretation by the authors of this report (without considering the final P&R approval decision indicated in the TPR).

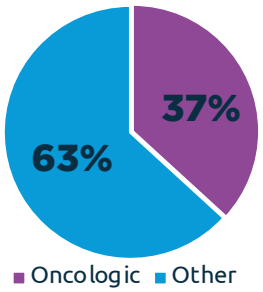
## 3.2 ESTABLISHMENT OF POTENTIAL RELATIONSHIPS OF VARIABLES WITH THE REIMBURSEMENT SITUATION OF ODS IN SPAIN

### Oncology ODs, compared to other therapeutic areas, would be more likely to be reimbursed

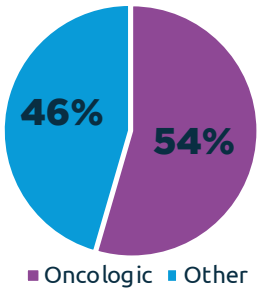
The defined clinical variables have been related with the reimbursement status of the ODs approved in Spain.

Results are shown by reimbursement category:

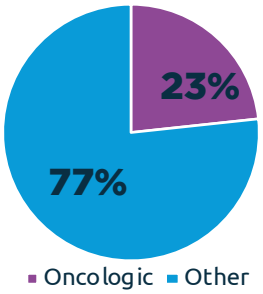
### THERAPEUTIC AREA




From the **P&R approved ODs**: **21** (37%) were indicated for **oncologic diseases**.

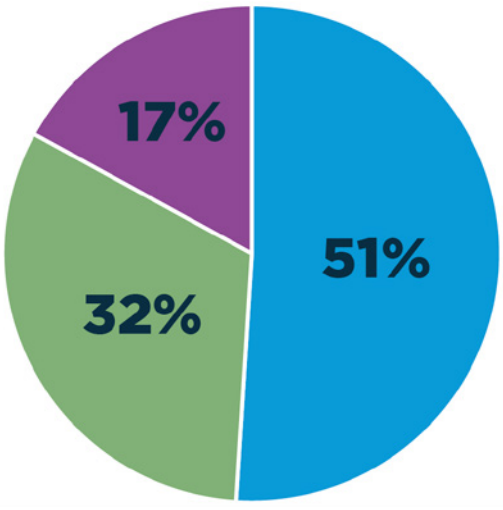



From the **under P&R decision ODs**: **13** (54%) were indicated for **oncologic diseases.**

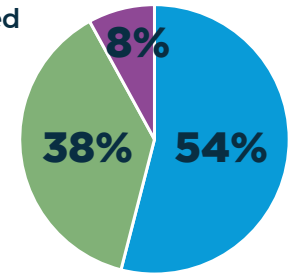



From the **P&R rejected ODs**: **7** (23%) were indicated for **oncologic diseases**.

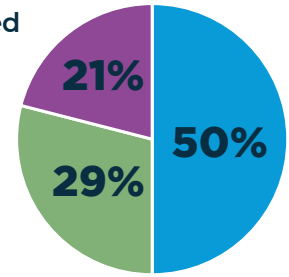
From the **ODs indicated for oncology disease**: **21** (51%) **had P&R approval** and 7 (17%) had P&R request rejected.




From the **ODs indicated for oncologic-hematologic disease**:



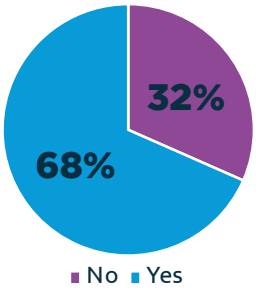

From the **ODs indicated for oncologic non-hematologic disease**:



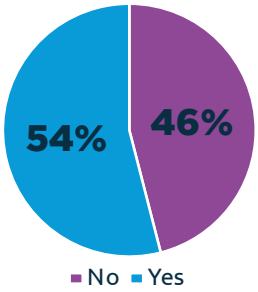

Reimbursed | Under P&R decision | Reimbursement rejected

## The absence of therapeutic alternatives would not influence the P&R decision

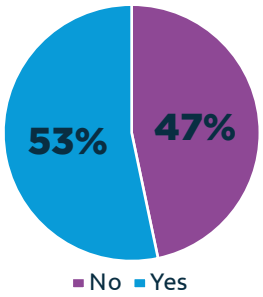
### EXISTENCE OF THERAPEUTIC ALTERNATIVES




From the **P&R approved ODs**: **18** (32%) didn't have a **therapeutic alternative.**

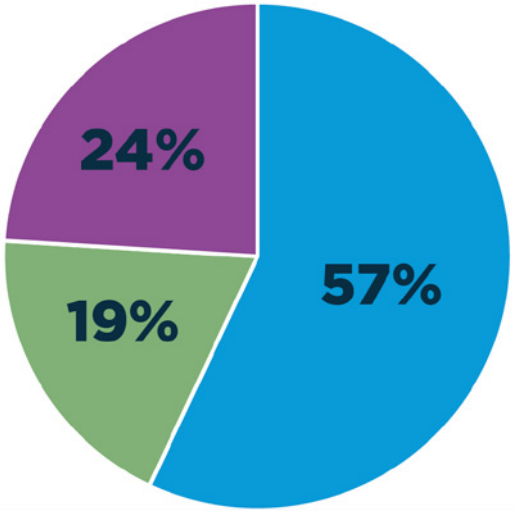



From the **under P&R decision ODs**: **11** (46%) didn't have a **therapeutic alternative.**

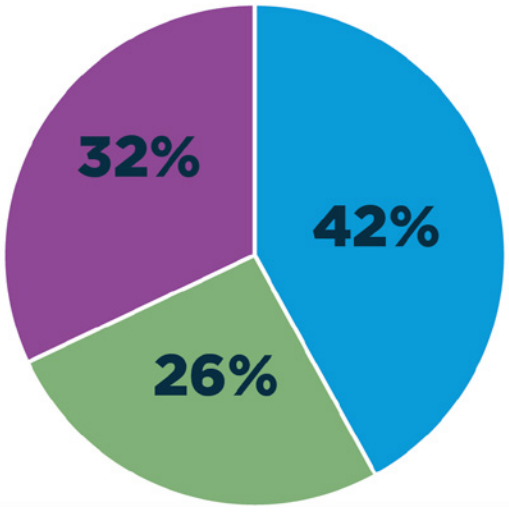



From the **P&R rejected ODs**: **14** (47%) didn't have a **therapeutic alternative.**

From the **ODs that had therapeutic alternative**: **39** (57%) **had P&R approval** and 16 (24%) had P&R request rejected.



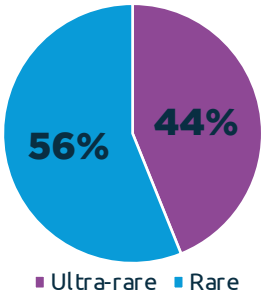

From the **ODs that did not have therapeutic alternative**: **18** (42%) **had P&R approval** and 14 (32%) had P&R request rejected



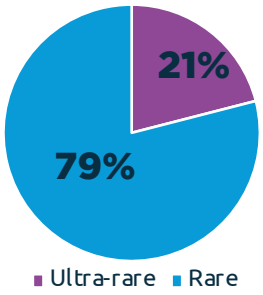

Reimbursed | Under P&R decision | Reimbursement rejected

## ODs indicated for ultra-rare diseases would be more likely to be reimbursed

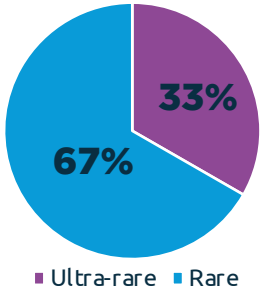
### RARITY OF DISEASE




From the **P&R approved ODs**: **25** (44%) were indicated for **ultra-rare diseases.**



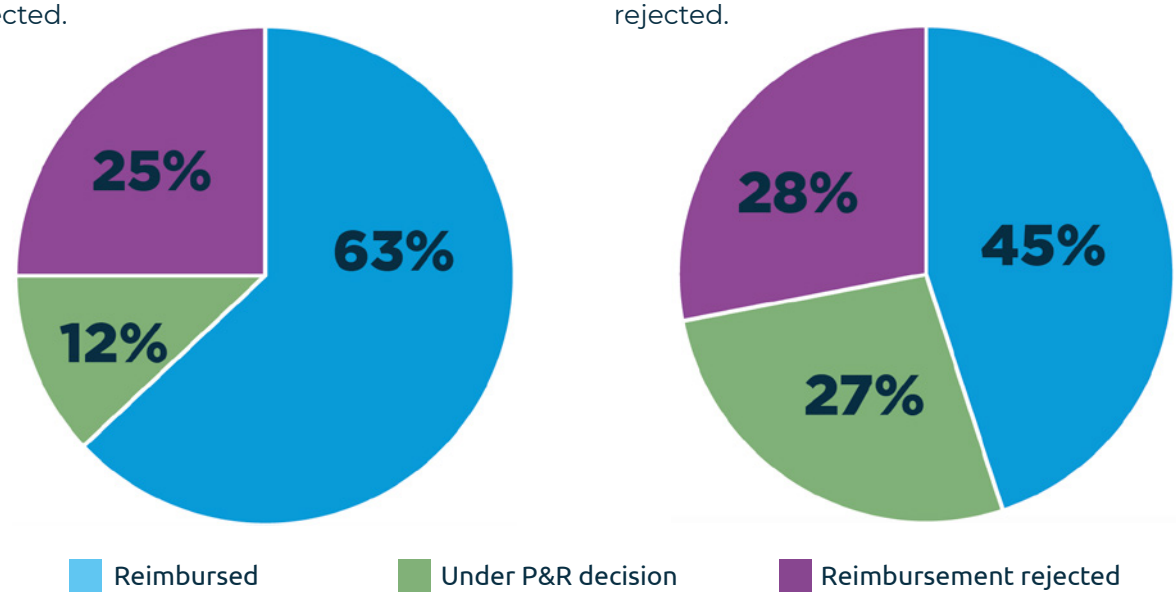

From the **ODs under P&R decision**: **5** (21%) were indicated for **ultra-rare diseases.**




From the **P&R rejected ODs**: **10** (33%) were indicated for ultra-rare diseases

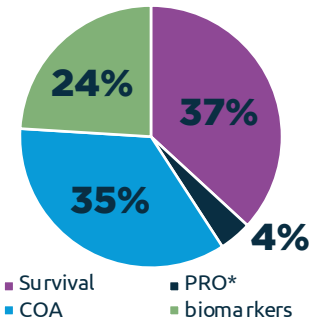
From the **ODs indicated for ultra-rare diseases** (<1/50.000 inhabitants): **25** (63%) **had P&R approval** and 10 (25%) had P&R request rejected.

From the **ODs indicated for rare diseases** (<5/10.000 inhabitants): **32** (45%) **had P&R approval** and 20 (28%) had P&R request rejected.

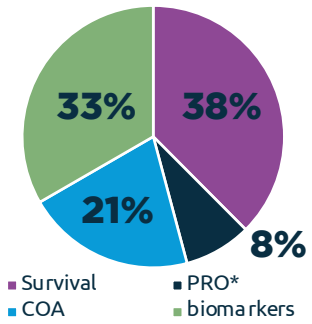


## ODs with survival-related outcomes would be more likely to be reimbursed

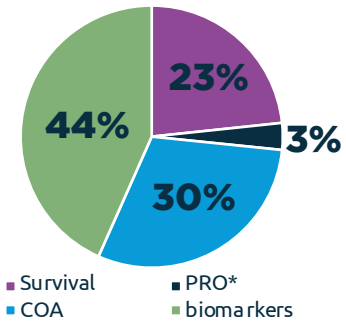
### OUTCOMES CLASSIFICATION




From the **P&R approved ODs**: **21** (37%) **have been evaluated with survival-related outcomes and 20** (35%) **with COAs*.**



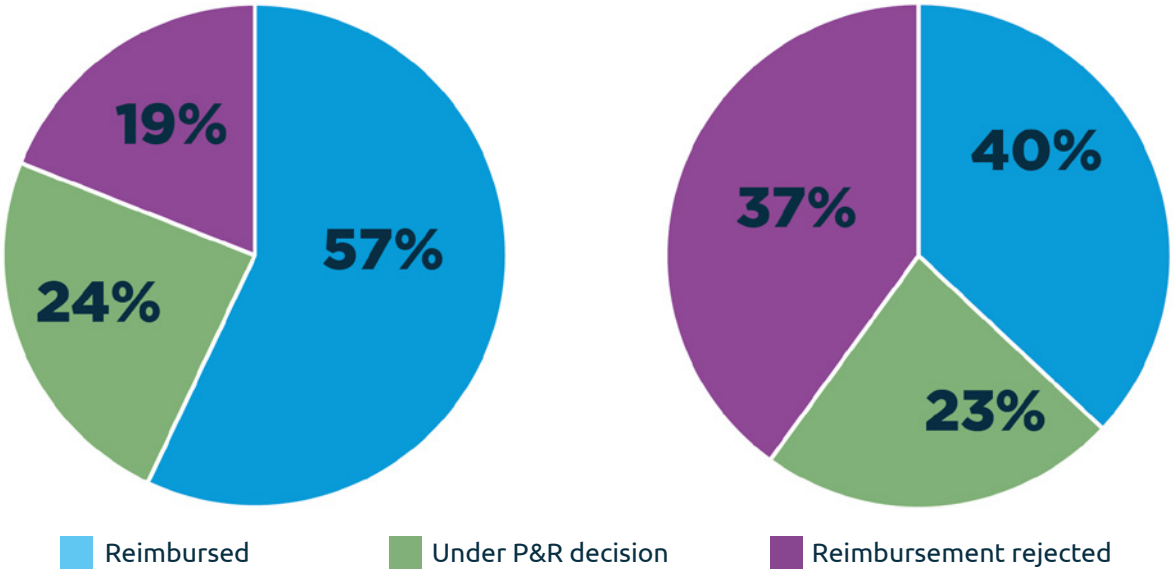

From the **ODs under P&R decision**: **9** (38%) **have been evaluated with survival-related outcomes and 8** (33%) **with biomarkers.**




From the **P&R rejected ODs**: **13** (44%) **have been evaluated with biomarker outcomes and 9** (30%) **with COAs*.**

From the **ODs with survival-related outcomes**: **21** (57%) **had P&R approval** and 7 (19%) had P&R request rejected.

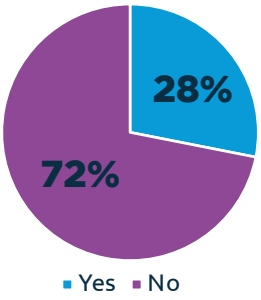
From the **ODs with biomarker outcomes**: **14** (40%) **had P&R approval** and **13** (37%) **had P&R request rejected**.



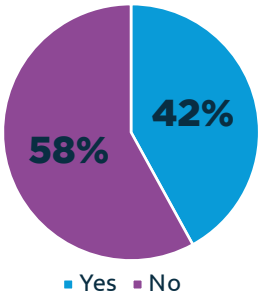

*Clinical outcomes assessment, *Patient-reported outcomes

## The requirement to have a PASS would not influence the P&R decision

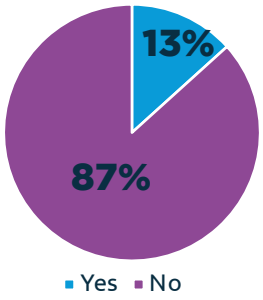
### SAFETY PROFILE




From the **P&R approved ODs**: **41** (72%) **did not have the obligation to conduct a PASS**.

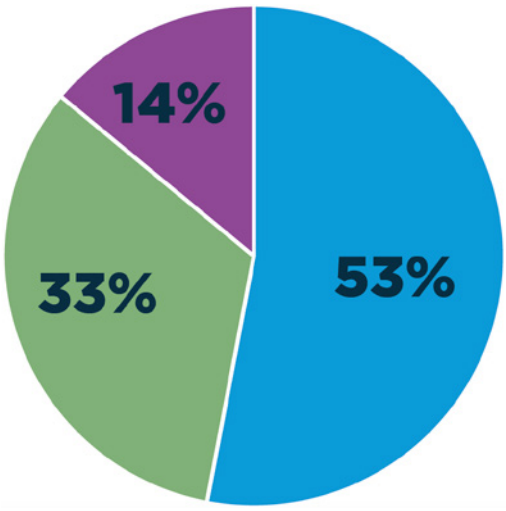



From the **ODs under P&R decision**: **14** (58%) **did not have the obligation to conduct a PASS**.

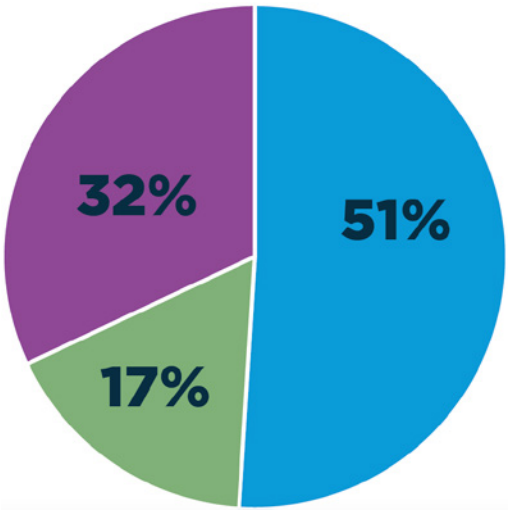



From the **P&R rejected ODs: 26** (87%) **did not have the obligation to conduct a PASS.**

From the **ODs that had the obligation to conduct a PASS: 16** (53%) **had P&R approval** and 4 (14%) had P&R request rejected.



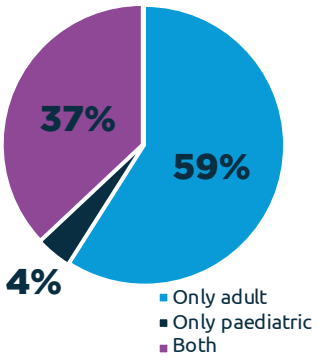

From the **ODs that did not have the obligation to conduct a PASS: 41** (51%) **had P&R approval** and 26 (32%) had P&R request rejected.



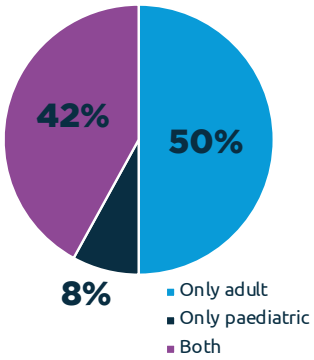

Reimbursed | Under P&R decision | Reimbursement rejected

## The type of population would not influence the P&R decision

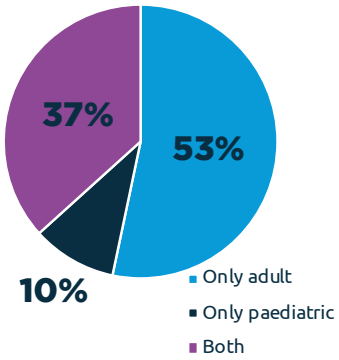
### TYPE OF POPULATION




From the **P&R approved ODs: 2** (4%) were indicated for **paediatric patients only**.

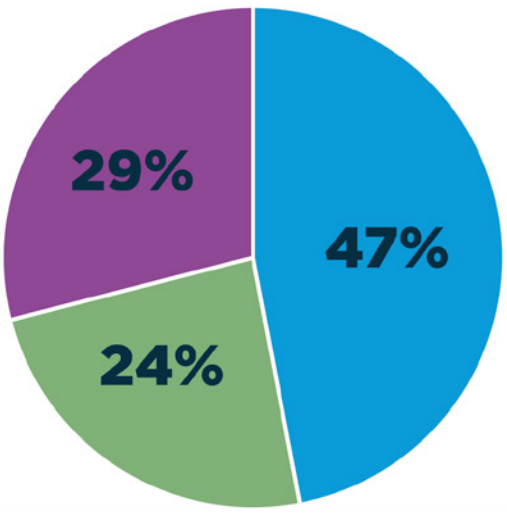



From the **ODs under P&R decision: 2** (8%) were indicated for **paediatric patients only**.

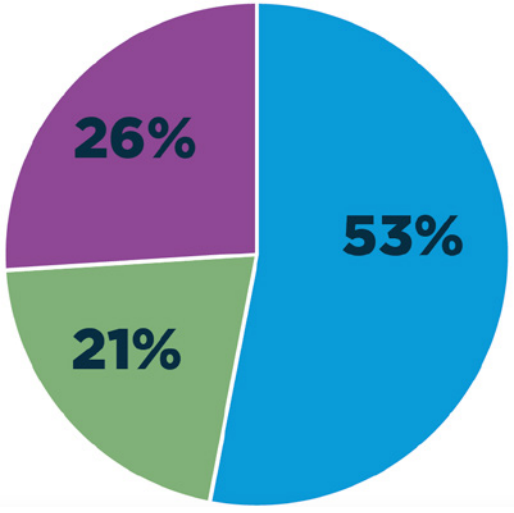



From the **P&R rejected ODs: 3** (10%) were indicated for **paediatric patients only.**

From the **ODs indicated for paediatric patients: 23** (47%) **had P&R approval** and **14** (29%) **had P&R request rejected**.




From the **ODs indicated for adults: 55** (53%) **had P&R approval** and **27** (26%) **had P&R request rejected.**




Reimbursed | Under P&R decision | Reimbursement rejected

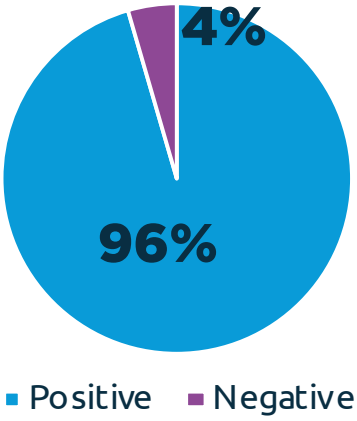
## ODs with positive TPR conclusion would be more likely to be reimbursed

The defined regulatory variables have been related with the reimbursement status of the ODs approved by the AEMPS.

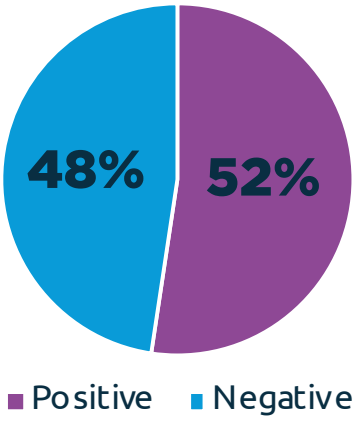
Results are shown **by reimbursement category**:

### TPR conclusion* (ODs with published TPR**)

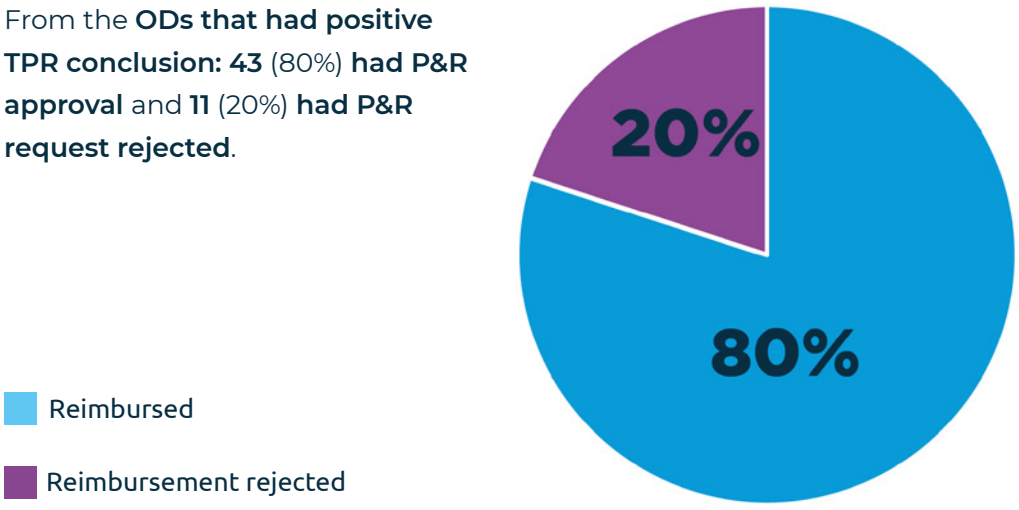
From the **P&R approved ODs: 43** (96%) had a **positive conclusion**.




From the **P&R rejected ODs: 11** (52%) had a **positive conclusion**.




From the **ODs that had positive TPR conclusion: 43** (80%) **had P&R approval** and **11** (20%) **had P&R request rejected**.

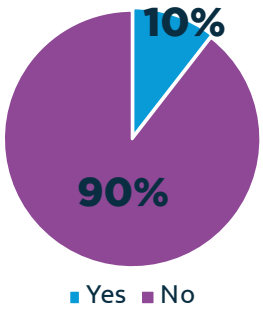



*The TPR conclusion refers to the final efficacy and safety conclusion of the ODs according to the TPR. This variable was based on a subjective interpretation by the authors of this report (without considering the final P&R approval decision indicated in the TPR).

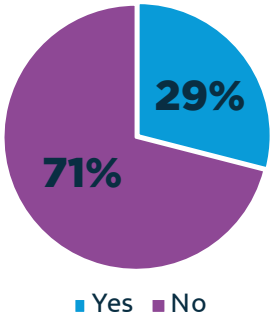
**The ODs under P&R decision process does not have published TPR.

## ODs without conditional approval would be more likely to be reimbursed

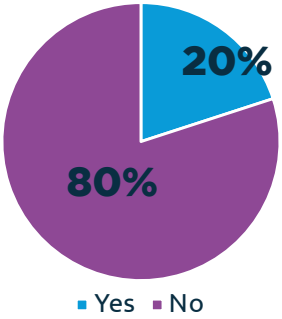
### CONDITIONAL APPROVAL




From the **P&R approved ODs**: **6** (10%) **were granted conditional approval** and **51** (90%) **were not granted conditional approval.**

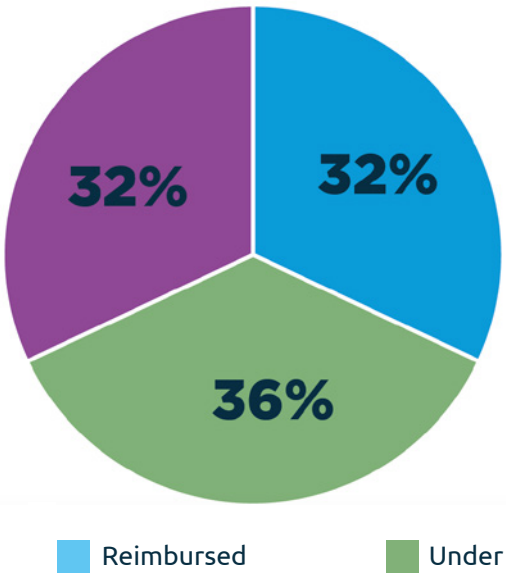



From the **ODs under P&R decision**: **7** (29%) **were granted conditional approval** and **17** (71%) **were not granted conditional approval.**

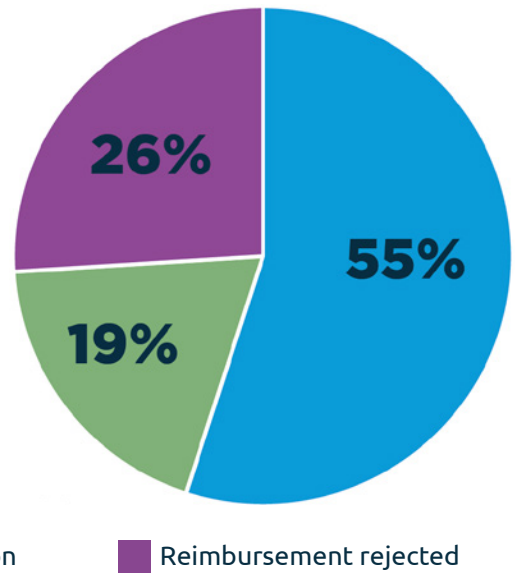



From the **P&R rejected ODs**: **6** (20%) **were granted conditional approval** and **24** (80%) **were not granted conditional approval.**

From the **ODs that were granted conditional approval: 6** (32%) **had P&R approval** and **6** (32%) **had P&R request rejected.**




From the **ODs that were not granted conditional approval: 51** (55%) **had P&R approval** and 24 (26%) had P&R request rejected.




Reimbursed | Under P&R decision | Reimbursement rejected

# Conclusions

## 01 Description of the Pricing & Reimbursement situation in Spain of Orphan Drugs approved by the European Commission:

Out of the **128 ODs approved by the European Commission, 111** (86,7%) ODs had been granted **marketing authorisation in Spain**.

Out of the **111 ODs** that had been granted **marketing authorisation in Spain, 57** (51,4%) had received **P&R approval, 24** (21.6%) were **undergoing the P&R process**, and **30** (27%) had their **P&R request rejected**.

## 02 Analysis of the administrative timelines of ODs in Spain:

There was a clear trend to **decrease in the administrative timelines from EC approval to Spanish marketing authorisation** from 2012 to 2021 (16,5 months vs 0,7 months). This would indicate that the administrative process in Europe and Spain might have been speeded up or that Marketing Authorization Holders would be asking for P&R in Spain sooner than in the past.

## Analysis of the impact of the TPR on the P&R evaluation of ODs in Spain:

Since the inclusion of the **Therapeutic Positioning Report** (a document issued by the Spanish Agency of Medicines that determines a new drug's relative positioning to what constitutes standard of care for the same indication to **inform P&R decisions in Spain**; TPR), in 2013, the **mean time** from **Spanish marketing authorization** to **P&R decision** was **18,2 months**, with a minimum of 3 months and a maximum of 50 months.

P&R evaluation timelines have been **slightly reduced** with the inclusion of TPRs by an **average of less than 1 month** since the inclusion of the TPR.

**The inclusion of the TPR during the P&R process hasn't shown to have a significant impact on P&R evaluation timelines of ODs in Spain.**

# 03 Description of the variables that would be relevant for the P&R process of ODs in Spain and establishment of potential relationships of variables with the reimbursement situation:

*Variables that would influence P&R decision:*

The **variables that would influence P&R decisions** for ODs in Spain were the **therapeutic area, the rarity of disease, the outcomes classification, TPR conclusion and the conditional approval:**

- **Therapeutic area**: From the 111 studied ODs, 41 (37%) were indicated for oncology diseases. From these, 21 (51%) were reimbursed and 7 (17%) had the P&R request rejected. **ODs indicated for oncology diseases, compared to other therapeutic areas, would be more likely to be reimbursed in Spain.**
- **Rarity of disease**: From the studied ODs, 40 (36%) were indicated for ultra-rare diseases (prevalence of <1/50.000 inhabitants). From these, 25 (63%) were reimbursed and 10 (25%) had the P&R request rejected. **ODs indicated for ultra-rare diseases would be more likely to be reimbursed in Spain.**
- **Outcomes classification**: From the studied ODs, 37 (33%) have been evaluated with survival-related outcomes. From these, 21 (57%) were reimbursed and 7 (19%) had the P&R request rejected. **ODs with survival-related outcomes would be more likely to be reimbursed.**
- **TPR conclusion:** From the studied ODs, 66 (33%) had a published TPR. Out of the 66 ODs with a published TPR, 54 (82%) had a positive TPR conclusion. From these, 43 (80%) were reimbursed and 11 (20%) had the P&R request rejected. **ODs with a positive TPR conclusion would be more likely to be reimbursed.**
- **Conditional approval**: From the studied ODs, 92 (83%) were not granted conditional approval by the EMA. From these, 51 (55%) were reimbursed and 24 (26%) had the P&R request rejected. **ODs without conditional approval would be more likely to be reimbursed.**

## *Variables that would not influence P&R decision:*

The **variables that would not influence P&R decisions** for ODs in Spain were the **existence of therapeutic alternatives**, the **type of population indicated and the requirement of a PASS:**

- **Existence of therapeutic alternatives**: From the studied ODs, 43 (39%) didn't have any therapeutic alternative. From these, 18 (42%) were reimbursed and 14 (32%) had the P&R request rejected. **The absence of therapeutic alternatives would not influence the P&R decision.**
- **Type of population**: From the studied ODs, 49 (44%)* were indicated for pediatric population and 104 (94%)* were indicated for adults. From ODs indicated for pediatric population, 23 (47%) were reimbursed and, from ODs indicated for adults, 55 (53%) were reimbursed. **The type of population would not influence the P&R decision.**
- **Requirement of a Post-authorization safety study (PASS)**: From the studied ODs, 30 (27%) had to conduct a PASS according to EMA and (81) 73% had not. From the ODs that had to conduct a PASS, 16 (53%) were reimbursed and, from ODs that had not to conduct a PASS, 41 (51%) were reimbursed. **The requirement to have a PASS would not influence the P&R decision.**
- **Economic variables** could not be assessed in this report because of a **lack of transparency**. Spain operates a dual pricing system for hospital medicines and the official listed prices in the available databases do not reflect the reimbursed price agreed with the Ministry of Health. The reimbursed prices are confidentially agreed between the Ministry of Health and the MAH.

*Including the ODs indicated for both (paediatrics and adults).

**Report by Omakase Consulting**

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