SOLVING THE MYSTERY: ARE THERE VARIABLES THAT COULD POSITIVELY INFLUENCE P&R APPROVAL OF ORPHAN DRUGS IN SPAIN?

HPR212

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BACKGROUND & OBJECTIVES

- P&R decision-making for orphan drugs (ODs) is faced with specific challenges, as the limited knowledge and heterogeneity of rare diseases make it difficult to demonstrate the added clinical benefit of a treatment[1,2]. Achieving approval from the European Commission (EC) does not guarantee access within the Spanish market. In Spain, the Committee on Pricing of Medicines and Healthcare Products (CIPM), responsible for the final pricing and reimbursement (P&R) decision, includes in their P&R resolutions the criteria used to justify such decisions. However, information on how these criteria are neither defined nor measured is not provided[3]. Therefore, the drivers influencing the approval or denial of a drug P&R are not clear[4].
- The objective of this study was to **identify the clinical and regulatory variables that might be relevant for the P&R decisions of ODs in Spain**.

METHODS

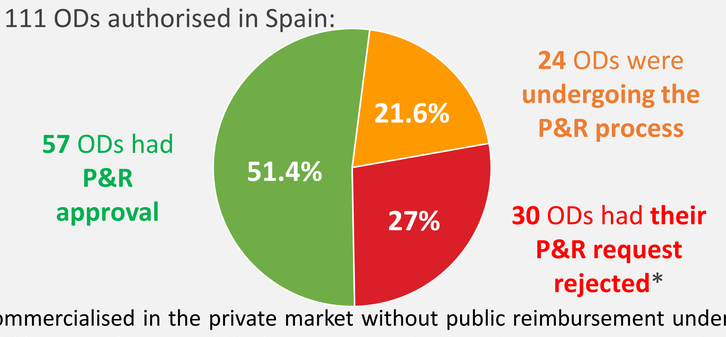
- This study includes ODs approved by the EC between 2006 and 2021 and that subsequently obtained Marketing Authorisation in Spain. ODs were classified according to their P&R status in Spain: approved, undergoing decision and rejected. P&R approval timelines in Spain were analysed.
- The potential variables that might influence reimbursement resulted from the official P&R criteria established by the Royal Decree Law 1/2015 of 24 July to evaluate the reimbursement of new drugs under the Spanish National Healthcare System (NHS) funds[4], as well as from the variables reported in the mandatory information that Marketing Authorisation Holders (MAHs) must provide to European and Spanish regulatory bodies as part of the Marketing Authorisation Application (MAA) and the national P&R request procedures.
- Variables included in the analysis were: therapeutic area, rarity of the disease, existence of alternative therapies, availability of survival-related outcomes, adequate safety profile, type of population, conditional approval status and a positive Therapeutic Positioning Report (TPR) conclusion. Economic variables have not been assessed due to lack of publicly-available information.

RESULTS

Orphan Drugs P&R status in Spain

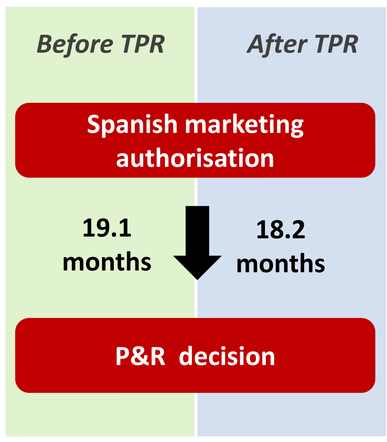
- A total of **128 ODs approved by the EC** between 2006 and 2021 were identified, **of which 111 (86.7%) have obtained marketing authorised in Spain**.

Out of the 111 ODs authorised in Spain:



*5 ODs were commercialised in the private market without public reimbursement under the NHS: Bronchitol®(mannitol), NexoBrid® (concentrate of proteolytic enzymes enriched in bromelain), Procysbi® (mercaptamine), Tobi Podhaler® (tobramycin) and Xermelo® (telotristat ethyl)

Regulatory timelines



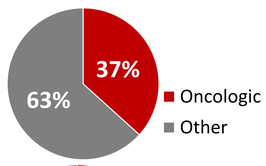
- In **May 2013**, the **Therapeutic Positioning Report** (TPR) was **introduced** as part of the **P&R process** in Spain. The TPR is an **evaluation document** issued by the Spanish Agency of Medicines and Medical Devices (**AEMPS**) that includes a review and summary of **relative (versus Standard of Care) efficacy and safety data** available for the **new product** to determine its **positioning in the treatment pathway**[5].
- The **inclusion of the TPR** during the P&R process **has not shown** a **significant impact** on **P&R evaluation timelines 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.** The mean time from Spanish marketing authorisation to P&R decision after introduction of TPR is 18.2 months (with a minimum of 3 months and a maximum of 50 months).

Clinical variables results

Out of the **111 ODs authorised in Spain**:

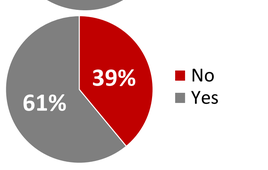
Therapeutic area

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



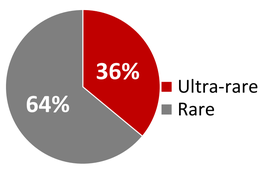
Existence of therapeutic alternatives

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



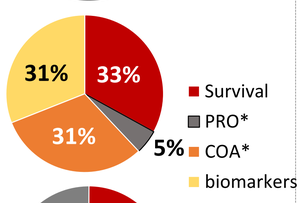
Rarity of disease

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



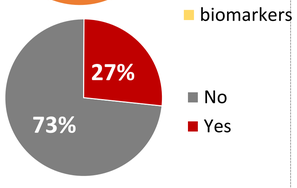
Outcomes classification

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



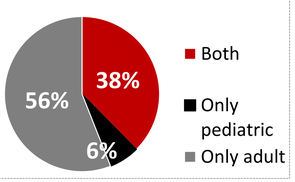
Safety profile

30 ODs (27%) had a European Medicines Agency (EMA) requirement to conduct a post-authorisation safety study (PASS)



Type of population

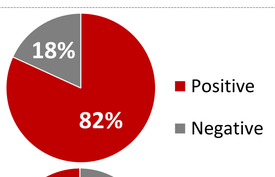
7 ODs (6%) were indicated for **paediatric patients only, 62 ODs (56%) for adults only** and **42 ODs (38%)** were indicated **for both** (adults and paediatrics).



Regulatory variables results

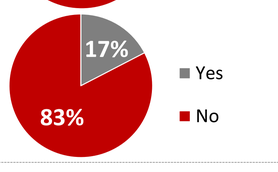
TPR conclusion

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



Conditional approval

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



Relationship of the clinical and regulatory variables with the reimbursement status

Out of the **111 ODs authorised in Spain**:

CLINICAL

Variables that seem to influence P&R decision:

- **Therapeutic area:** For **ODs indicated for oncology diseases, 21 (51%)** were **reimbursed and 7 (17%) had their P&R request rejected**.
- **Rarity of disease:** For **ODs indicated for ultra-rare diseases, 25 (63%)** were **reimbursed and 10 (25%) had their P&R request rejected**.
- **Outcomes classification:** For **ODs evaluated with survival-related outcomes, 21 (57%)** were **reimbursed and 7 (19%) had their P&R request rejected**.

Variables that seem not to influence P&R decision:

- **Existence of therapeutic alternatives:** For **ODs that did not have any therapeutic alternative, 18 (42%)** were **reimbursed and 14 (32%) had their P&R request rejected**.
- **Safety profile:** For **ODs that did not require a PASS study, 41 (51%)** were **reimbursed**. For **ODs that required a PASS study, 16 (53%) were reimbursed**.
- **Type of population:** For **ODs indicated for paediatric population, 23 (47%) were reimbursed** and, for **ODs indicated for adults, 55 (53%) were reimbursed.**

REGULATORY

Variables that seem to influence P&R decisions:

- **TPR conclusion: For ODs with a positive TPR conclusion, 43 (80%) were reimbursed and 11 (20%) had their P&R request rejected.**
- **Conditional approval: For ODs without conditional approval granted by the EMA, 51 (55%) were reimbursed and 24 (26%) had their P&R request rejected.**

CONCLUSIONS

- From all ODs approved by the EC between 2006 – 2021 and which have obtained MAA in Spain, **57 (51.4%)** were **reimbursed**, **30 (27%)** were **rejected and 24 (21.6%)** were **undergoing decision with the potential to be reimbursed in the future**.
- **Before the inclusion of the TPR in 2013**, the **mean time** from Spanish marketing authorisation to P&R decision **was 19,1 months** and **after the TPR inclusion**, the **mean time** decreased to **18,2 months**. **P&R evaluation timelines** have been **slightly reduced** since the inclusion of TPRs by an **average of less than 1 month**.
- ODs **might be more likely to be reimbursed** in Spain if they have a **positive TPR conclusion** (80% were reimbursed), if indicated for an **ultra-rare disease indication** (63% were reimbursed), if their clinical programme is based on **survival-related outcomes** (57% were reimbursed), if they are approved **without conditional approval** (55% were reimbursed) and if directed to an **oncology indication** (51% were reimbursed).
- **Economic variables could not be assessed in this study because of lack of transparency in public sources**. Spain operates a **dual pricing system** for hospital medicines and the **official listed prices** in the **available** databases **do not reflect the real reimbursed prices,** since **these are confidentially agreed between the Ministry of Health and the MAH**.

REFERENCES

[1]Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J Rare Dis. 2011;6(42); [2]Drummond, M. F., et al. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;(23):36–42; [3]BOE. Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios. [Internet]. *Available from*: https://www.boe.es/buscar/act.php?id=BOE-A-2015-8343; [4]Calleja MÁ, Badia X. Feasibility study to characterize price and reimbursement decision-making criteria for the inclusion of new drugs in the Spanish National Health System: the cefiderocol example. Int J Technol Assess Health Care [Internet]. 2022;38(1). Available from: https://doi.org/10.1017/S0266462322000332; [5]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