ARE P&R OFFICIAL CRITERIA RELATED WITH REAL P&R APPROVAL OF ORPHAN DRUGS (ODs) IN SPAIN?

Badia X[1], Gil A[1], Shepherd J[1], Guarga L[1]
[1]Omakase Consulting, Barcelona, Spain.

BACKGROUND & OBJECTIVES

P&R of ODs is a challenging process, as the limited knowledge and heterogeneity of the diseases make it difficult to demonstrate the added clinical benefit of an OD [1]. This problem, added to the fact that ODs often fail to meet accepted cost-effectiveness criteria [2,3], has led to a number of exceptions the way ODs are appraised and resulted in differences between countries regarding clinical requirements and evaluations [1,4] .The aim of this work is to identify if the official criteria of Spanish P&R process are related with P&R approval for ODs.

METHODS

ODs approved by the European Commission between 2012 and 2016 were classified according to their P&R status in Spain (reimbursed, undergoing decision and rejected). Hypotheses on likelihood of reimbursement for ODs were formulated based on the P&R official criteria established by Royal Decree Law 1/2015 of 24 July:

P&R official criteria

1. Disease severity
2. Unmet needs of certain collectives
3. Existence of alternative
4. Degree of innovation
5. Cost-effectiveness (CE)
6. Budget Impact (BI)

Hypotheses on likelihood of reimbursement

1. Oncologic vs. non oncologic indication and to the availability of direct clinical trial outcomes
2. Indicated for ultra-orphan diseases affecting <1/50000 inhabitants
3. ODs without a therapeutic alternative for the approved indication
4. ODs with a published Therapeutic Positioning Report (TPR) with a positive opinion, meaning that the drug offers an added therapeutic value

Two additional reimbursement variables related to the Spanish P&R process were formulated: reimbursement in the EU4 countries, as Spain uses external reference pricing in innovative medicines, and the ODs marketing authorisation holder (MAH) to be listed in the Spanish Profarma Plan (SPP), thus contributing to the GDP. CE and BI were not assessed in this study because of lack of information. The validity of the hypotheses were tested through a statistical analysis using regression models [5] (Probit, Logit and OLS) and Random Forest analysis [6].

RESULTS

- A total of **40** ODs were identified that had been approved by the EC between 2012-2016 and with marketing authorisation in Spain.
- From the identified ODs, **17** (**42.5%**) were reimbursed, **16** (**40%**) were undergoing reimbursement decision and **7** (**17.5%**) had reimbursement rejected.
- Potential variables that could influence reimbursement were classified according to the system described by Zozaya et. al. [7] based on criteria for reimbursing orphan medicinal products.

Clinical variables

Fig. 1: Oncologic ODs (**n=18, 45%** of studied ODs)

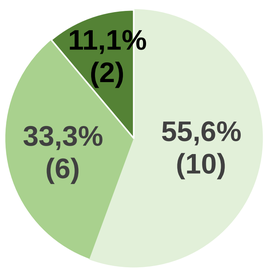


Fig. 2: ODs without existing therapeutic alternative (**n=16, 40%** of studied ODs)

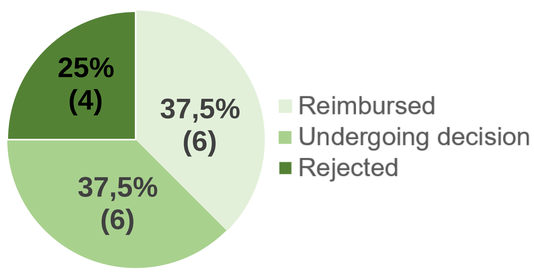


Fig. 3: ODs indicated for ultra-rare diseases (**n=13, 35.1%** of studied ODs)

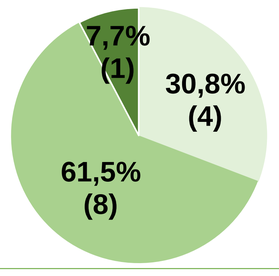
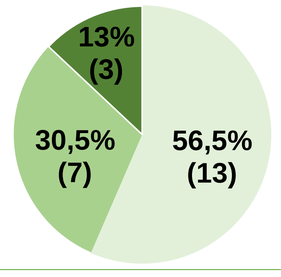
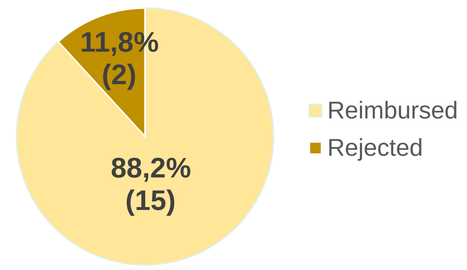


Fig. 4: ODs with directs outcomes **(n=23, 57.5%** of studied ODs)



Institutional variables

Fig. 5: ODs with published TPRs with positive opinions (**n=17, 81%** of the 21 ODs with a published TPR)



Economic variables

Fig. 6: ODs reimbursed in France, Italy or the UK (**n=26, 65**% of studied ODs)*

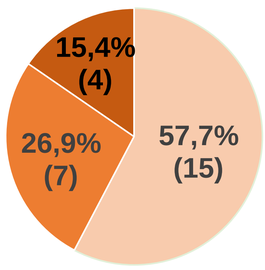
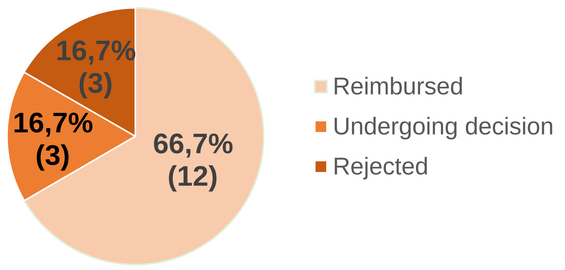


Fig. 7: ODs with MAH included in the Profarma Plan (**n=18, 45%** of studied ODs)



* Germany was excluded from the results analysis as ODs in Germany are reimbursed as soon as they enter the German market.

- Statistical analyses: a Probit regression model [8] was used to predict the impact of the studied variables on reimbursement in Spain and results were checked with a second analysis, an algorithm called Random Forest [9].

Figure 1: Results from the Probit model used to predict the potential impact of studied variables in the reimbursement approval of ODs in Spain

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Probit regression                               Number of obs   =         23
                                                LR chi2(4)      =       5.81
                                                Prob > chi2     =     0.2136
Log likelihood = -11.227401                     Pseudo R2       =     0.2056
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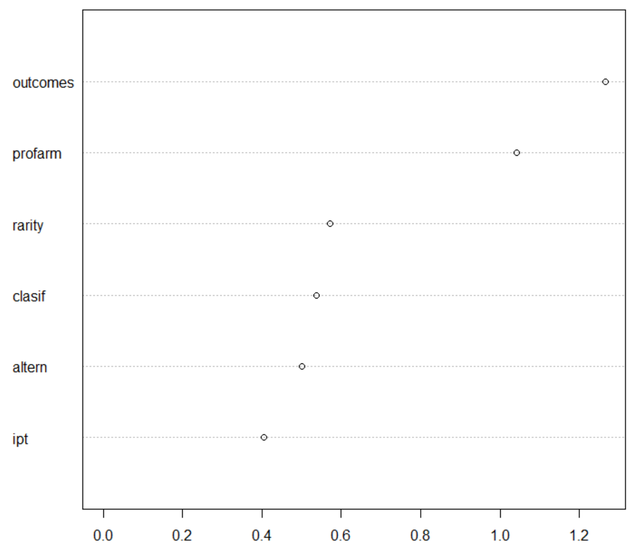
reim	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ipt	-5.21e-12	1.201692	-0.00	1.000	-2.355273	2.355273
profarm	2.461858	1.469033	1.68	0.094	-.4173939	5.341111
outcomes	-1.536857	.8697015	-1.77	0.077	-3.241441	.1677266
clasif	-2.321829	1.790624	-1.30	0.195	-5.831388	1.187729
_cons	2.305285	1.685992	1.37	0.172	-.9991974	5.609768

Clasif: Therapeutic Area Classification; ipt: Therapeutic Positioning Report; outcomes: Clinical Outcomes Classification; profarm: Profarma Plan; Reim: Reimbursement.

Figure 2: Results from the Random Forest analysis used to predict the potential impact of studied variables in the reimbursement approval of ODs in Spain



Altern: Therapeutic alternative; Clasif: Therapeutic Area Classification; ipt: Therapeutic Positioning Report; outcomes: Clinical Outcomes Classification; profarm: Profarma Plan; Rarity: rarity of disease; Reim: Reimbursement.

- All statistical analyses were consistent with the results, showing that two variables have an impact on reimbursement. The variables that can affect reimbursement are:
  - ✓ **Clinical trial outcomes classification** (p<0,077): a less direct or indirect outcome decreases the probability of reimbursement.
  - ✓ **Manufacturer included in the SPP** (p<0,094): the MAH of an OD to be included in the PP increases the probability of reimbursement.

CONCLUSIONS

Official P&R criteria are not always used by national authorities to reimburse an OD, as only for ODs to have less direct or indirect clinical trial outcomes showed to negatively influence reimbursement and the inclusion of the OD's manufacturer in the SPP showed to positively influence reimbursement. Budget Impact would be an important variable for reimbursement, but could not be assessed as information about sales forecast isn't public and published prices don't match the real ODs price.

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