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Determinants of price negotiations for new drugs. The experience of the Italian Medicines Agency

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ABSTRACT

Objectives: The aim of this paper is to investigate the determinants of the difference between the price proposal submitted by the industry and the final negotiated price. We used Italy as a case-study.
Methods: Data were gathered through the information system used by Italian Medicines Agency. The time-frame for this analysis is 2013–2017. Factors influencing the delta price were analyzed through a regression analysis.
Results: 44 orphan drugs and 89 new other molecular entities obtained reimbursement in the last five years. Following the negotiation process, prices were lowered by 25.1% and 28.6% on average for orphan drugs and other molecules respectively. The price reduction was higher for innovative drugs (-32.2%). Statistically significant determinants associated to higher price reduction were: i) the implementation of a product specific monitoring registry, ii) the negotiation of a financial-based Managed Entry Agreement, iii) a target population larger than 20,000 patients, iv) an expected National Health Service expenditure larger than €200 million.
Discussion: The impact of some variables on the delta price was predictable (e.g. for drugs with an expected higher budget impact and a larger population target), others were more surprising (e.g. a significant price reduction for "innovative" drugs). The implementation of financial-based agreements, which often rely on confidential arrangements, was one of the determinants with higher impact on price reduction.

1. Introduction

Pharmaceutical price regulation should pursue both static and dynamic allocative efficiency. Price-competition should be enhanced for drugs with a similar risk-benefit profile and a premium price should be guaranteed to products that provide added value [1]. Value-based pricing (VBP) has been advocated to reach this goal. The debate over VBP has been raised in the US [2–4], where prices are still unregulated, but discounts over list prices are quite diffused among insurance companies. However, the debate on VBP has mainly affected those countries where prices are directly or indirectly regulated. VBP requires that benefits and costs are identified, measured and evaluated, that benefits are aggregated and that a decision rule is taken to convert benefits in an acceptable cost, given the budget constraints. Different models operationalizing VBP under budget constraints are currently used, ranging from a threshold over the cost per QALY (Quality Adjusted Life Years) to a multi-criteria approach where different domains (including disease severity, unmet need, therapeutic added value, impact on unit cost per patient, budget impact) are considered to negotiate drugs prices [5,6]. This negotiation, which is in most countries confidential may bring out a mis-alignment between the value proposition by the industry and the value perception under budget constraints of payers. As a result, there could be an important gap between the list price proposal submitted by the industry and the final negotiated price (hereafter "ΔP"). There is no evidence, to our best knowledge, on the drivers of this gap.

Italy is one of the countries where the drugs prices are regulated through negotiation and represents an ideal case-study for four reasons.

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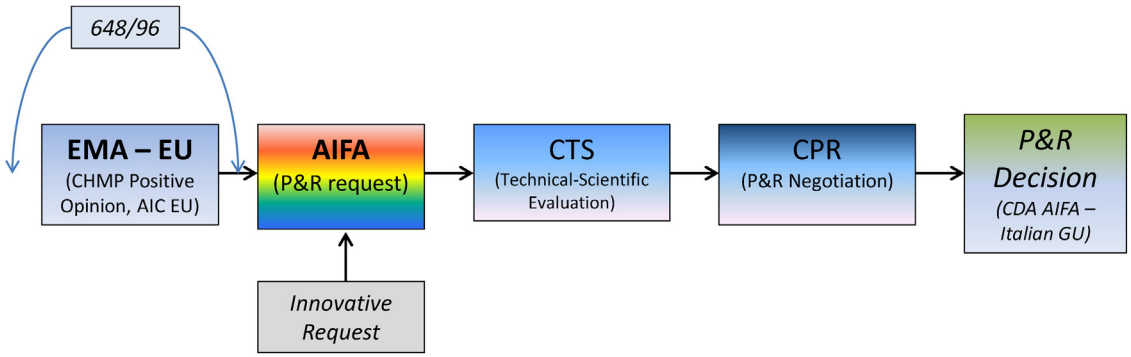

Fig. 1. Overview of the P&R procedure to follow to market a medicinal product in Italy.

First, price and reimbursement (P&R) for new medicines are simultaneously negotiated by the Italian Medicines Agency (AIFA) [7] and the relevant company. This makes tougher the negotiation, since a drug will not get reimbursement if an agreement on price is not reached. The P&R process is described in Box 1 (supplementary material) and Fig. 1.

Second, Italy is among those countries which rely on a multi-criteria approach in the negotiation. The ΔP cannot be ascribed to a single reason (i.e. prices that make the Incremental Cost-Effectiveness Ratio overcoming the relevant threshold).

Furthermore over the last decade, the AIFA has extensively relied on Managed Entry Agreements (MEAs) [10]. MEAs are arrangements between manufacturers and payers that enable access to health technology subject to certain conditions. They have been addressed to manage the uncertainty over the clinical and economic impact of drugs [11]. These agreements can be divided into two groups: financial agreements, which allow payers to share with the industry the post-marketing budget impact of new drugs; outcome-based agreements, that link payers' commitment to the actual impact of the drugs on health [12]. In Italy both financial-based and outcome-based contracts are used. The former includes hidden discounts, discounts on a predefined number of first cycles/packages (named in Italy cost-sharing), spending caps on each single drug and price/volume agreements; the latter includes performance-linked reimbursement contracts, which limit reimbursement to patients responding to the treatment (named in Italy payment-by-result or risk-sharing) [13]. Cost-sharing, payment-by-results and risk-sharing rely on monitoring registries implemented by AIFA, which allow to track each single patient in the real world setting and collect data needed for the purpose of the agreement [14]. In Italy, as well as in other healthcare systems, MEAs and negotiated price discounts are confidential [15].

Finally, early access programs for drugs are quite well established in Italy, including compassionate use, which is covered by the industry, and off-label use reimbursed by the National Health Service (NHS). Off-label use is allowed by AIFA (in given circumstances) and provides for data collection before the drug enter the negotiation process, thus possibly reducing uncertainty (see Box 2 - supplementary material).

For these reasons we used the Italian case-study to explore to what extent the price initially proposed by companies is lowered during the negotiation, and to investigate the determinants of the difference between such price proposal and the final reimbursed price.

2. Methods

This analysis includes all new drugs whose P&R process was concluded in the last 5 years (2013–2017) with a positive decision on reimbursement. We have distinguished between orphan drugs, whose prices are usually higher, given the small patient populations, and all the other new molecules. Only new molecular entities were included in the analysis, therefore excluding extensions of therapeutic indications, cause the negotiation of an indication extension already starts from a price published in the Italian Official Gazette and that this price is often requested by the companies.

Data gathering relied on European Medicines Agency's website (EMA), the AIFA information system which tracks all P&R submissions, the P&R dossiers, minutes from the two committees' meetings (Scientific-Technical Committee (CTS) and Price and Reimbursement Committee (CPR)) and the official documentation, revised by AIFA's Management Board (CDA), regarding the outcome of the negotiation.

Table 1
Orphan drugs whose companies have made a request for price and reimbursement in Italy between 2013 and 2017.

New Orphan Drugs TOT = 66	REIMBURSED	NOT REIMBURSED	STILL NEGOTIATING
	44 (66.7%)	11 (16.7%)	11 (16.7%)
Marketing Authorization (EMA)			
Full Authorization	33	5	7
Authorization Under Exceptional Circumstances (UEC)	2	3	3
Conditional Marketing Authorization (CMA)	9	2	1
Withdrawn Authorization	0	1	0
Innovation Status			
Full	5	1	0
Potential	3	0	2
None	36	10	9
Previously reimbursed through Law N.648/96			
	4	2	1
Compassionate Use			
	11	3	3

Table 2
Overview of the new molecular entities (non-orphans) that have made a request for price and reimbursement in Italy between 2013 and 2017.

New Molecular Entities (not orphan) TOT = 130	REIMBURSED	NOT REIMBURSED	STILL NEGOTIATING
	89 (68.5%)	17 (13.1%)	24 (18.5%)
Marketing Authorization (EMA)			
Full Authorization	87	16	23
Authorization Under Exceptional Circumstances (UEC)	2	0	0
Conditional Marketing Authorization (CMA)	0	0	1
Withdrawn Authorization	0	1	0
Innovation Status			
Full	10	0	0
Potential	5	0	0
None	74	17	24
Previously reimbursed through Law N.648/96			
	5	1	0
Compassionate Use			
	14	1	2

A regression analysis was performed using SAS software (Inc. SI. SAS software, Version 9.4 of the SAS System for Windows. 2016) to evaluate variables influencing the ΔP.

With regards to pricing, if the company presented different price per unit, the highest one was chosen. The final price incorporates hidden discounts and the expected financial impact of financial-based MEAs (cost-sharing, spending caps, price/volume agreements) and outcome-based MEAs associated with monitoring registries (payment-by-result and risk-sharing). To calculate the expected financial impact of financial-based and outcome-based MEAs, the Java program "Plot Digitizer" (GNU Library or Lesser General Public License version 2.0 (LGPLv2) GGPL version 2. (GPLv2). Plot Digitizer. 2016. https://sourceforge.net/projects/plotdigitizer/) was used (see Annex 1 - supplementary material). The proposed price was compared to the final price including the effects of MEAs. Finally, the overall price reduction was provided by the Statistical Analysis.

The impact of the following independent variables on the ΔP was considered for the analysis: orphan status (*yes/no*), size of the pharmaceutical company submitting the P&R dossier (*SME–small medium enterprise / Big Pharma*), type of EMA Marketing Authorization (*full / conditional / under exceptional circumstances*), use or non-use and type of MEAs -excluded hidden discounts- (*no MEA / outcome-based / financial-based*), establishment of a drug registry (*yes / no*), innovativeness status (*full / potential / none*), prior inclusion of the drug in the list of off-label medicinal products based on the Italian law 648/96 before the regular P&R negotiation process took place (*yes / no*), prior compassionate use of the drug (*yes / no*), AIFA assessment process (*ordinary / accelerated*), expected target population in the first three years of commercialization in Italy (categorized as: *0–500 / 500–3000 / 3,000–20,000 / >20,000 patients*), and predicted NHS expenditure in the first three years on the Italian market (categorized as: *0–15Mln / 15-50Mln / 50-200Mln / >200Mln€*) (see Table 4). The two latter variables are quoted in the P&R dossier and estimated by the submitting company. These two variables have been treated as categorical allowing to capture more complicated relationships than the linear one, where it is implicitly assumed that each unit change has the same effect on the dependent variable. When creating categories, the empirical distribution of the variable has been considered.

The impact of each variable on delta-price was firstly investigated using a univariate approach (one-way ANOVA), assuming that the hypotheses on which the model is based hold.

Subsequently, a multivariate model was built to assess how these factors, taken into account simultaneously, influence the ΔP, considered as a proxy of the result of the final price negotiation process. In addition to the variables described above, the beginning year of the negotiation process has been included in the multivariate model to account for the possible confounding due to time. In order to select the "best" subset of predictors to be included in the final model, a backward elimination approach was used (the backward elimination has been run manually). Then an automatic backward selection has been performed using an appropriate statistical SAS software tool to verify the consistency of the results obtained with the two procedures. A complete case analysis has been performed, since the hypothesis of a non-informative missing mechanism in the data is reliable. Given the confidential nature of data, they are presented as aggregate results.

3. Results

The number of submitted dossiers was 66 and 130 for orphan and non-orphan drugs (new molecular entities) respectively. Reimbursement was granted to 66.7% of orphan drugs (44) and 68.5% of non-orphans (89), while 16.7% (11) and 13.1% (17) respectively were not reimbursed (Tables 1–2). The other products, 11 orphans (16.7%) and 24 non-orphans (18.5%), were still in the negotiating phase. Moreover, the Marketing Authorization of two of these products (an orphan and a non-orphan) was withdrawn from the European market. The status of "innovative drug" was given to 8 orphan reimbursed products (5 classified as fully innovative and 3 as potentially innovative), to 1 non-reimbursed orphan medicinal product and to 2 drugs still under negotiation (potentially innovative) (Table 1 – Fig. 2); out of the non-orphans, the innovative status was given to 15 reimbursed products (10 classified as fully innovative and 5 as potentially innovative) (Table 2 – Fig. 2). Furthermore, 7 orphan drugs and 6 non-orphans were previously included in the list of off label drugs based on the Italian law 648/96 before a regular P&R negotiation process took place, and 17 of each group were prior prescribed through compassionate use (Table 1–2).

In general all agreements made during the establishment of the price for reimbursed products have allowed to lower the proposed price by 27.4% on average (Table 3). In particular, the status of "innovative drug" was granted to 24 medicinal products (23 drugs reimbursed by the NHS and 1 non-reimbursed drug) (Table 1–2). The average ΔP for these drugs was 32.2% (Table 3). The average ΔP for reimbursed orphan and non-orphan drugs was 25.1% and 28.6% respectively (Table 3).

The univariate analyses of possible determinants of the ΔP show that a previous inclusion in the list of off label drugs based on the Italian law 648/96, the establishment of a drug monitoring registry, the use of MEAs, the target population and the expected NHS expenditure have a statistically significant impact on the ΔP. In particular, the first one reduces the ΔP, the others increase it (use of a Monitoring Registry, use of a financial-based MEA, target population <20,000, expected expenditure <200 Mln €). On the other hand, the orphan status, the size of the pharmaceutical company, the type of EMA authorization, the type of AIFA assessment pro-

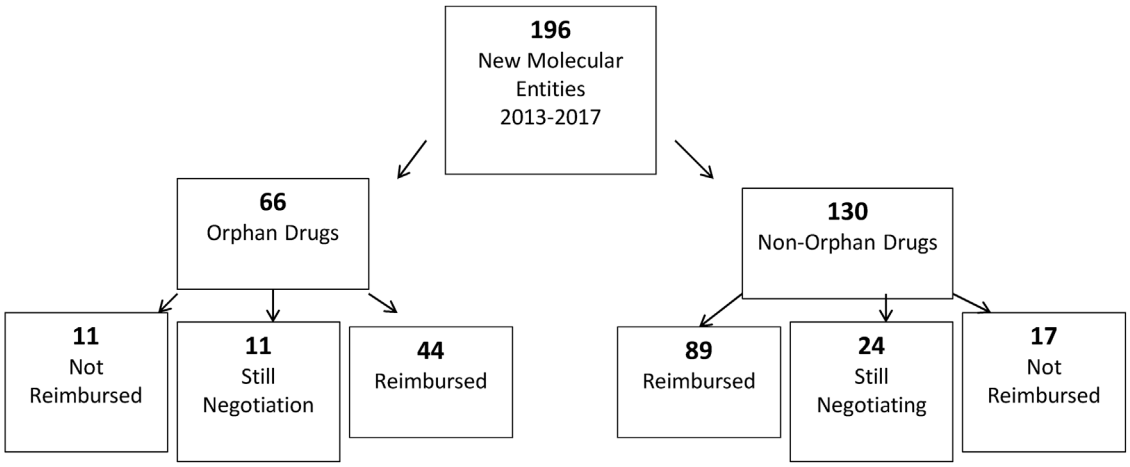

Fig. 2. Overview of all new drugs that have required P&R in Italy in the last 5 years (2013–2017).

Table 3
Overview of the impact that the negotiation of all agreements had on the price of novel drugs in 2013–2017 in Italy.

	New Drugs 2013-2017*	average **ΔP** (average of the difference between the final price negotiated with AIFA and the price proposed by the company)
All Reimbursed Drugs	**133**	**−27.4%**
Reimbursed	44	**−25.1%**
Orphan Drugs		
Reimbursed	89	**−28.6%**
New Molecular Entities		
Reimbursed	23	**−32.2%**
Innovative Drugs		

* all new drugs whose P&R process in Italy was concluded in the last 5 years (2013–2017) with a positive decision on reimbursement.

cess, the innovative/potentially innovative status of the drug, and the previous compassionate use of the drug, are not statistically significant (see online supportive information -Annex 1- for further details).

In the multivariate regression analysis, as a result of the backward elimination process [24], three variables were selected for the final model as the "optimal" subset of variables that explain the delta-price variability: the prior inclusion in the list of off label drugs based on the Italian law 648/96, the implementation of a MEA, and the expected expenditure in the first three years on the market (see Table 5). Due to some missing values in the expected expenditure variable, the results of this analysis are based on 122 out of 133 drugs.

In Table 6 results of the multivariate analysis are shown. Overall, the mean decrease of the final price with respect to the proposed price for the drugs which were not previously included in the list of off label drugs based on the Italian law 648/96, for which no MEAs were applied and with an expected expenditure of 0–15 Mln € (the reference category in the present analysis) is 26.2% (the intercept of the model). The prior inclusion in the list of off label drugs based on the Italian law 648/96, the application of a financial-based MEA and a higher expected expenditure in the first three years of commercialization, produce a decrease of that mean ΔP by 11.9%, an increase of ΔP difference by 10.3% and an increase in ΔP by 14.4% respectively.

Overall, this regression model shows a quite low explanatory potential since the explained percentage of the variability of the response data around its mean is about 15% (the adjusted R-square value).

Table 4
Overview of the one-way ANOVA analyses for delta-price.

Variable	N Obs	Mean	Std Dev	F	p-value
Orphan Drug Status				0.96	0.3290
no	89	−28.2	18.44		
yes	44	−24.9	16.42		
Size of Pharmaceutical Company				0.13	0.7216
Big Pharma	126	−27.0	17.88		
SME	7	−29.4	17.34		
EMA Authorization				0.06	0.9372
conditional	9	−26.7	16.10		
under exceptional circumstances	4	−24.0	24.39		
full	120	−27.2	17.85		
AIFA assessment process				0.66	0.4178
accelerated	82	−28.1	18.63		
ordinary	51	−25.5	16.43		
Innovativeness Status				0.80	0.4535
none	110	−26.4	16.88		
potential	8	−27.0	7.15		
full	15	−32.5	26.58		
Inclusion on list for Law 648/96*				4.06	0.0458
no	124	−27.9	18.03		
yes	9	−15.7	8.44		
Registry*				6.54	0.0117
no	70	−23.4	15.05		
yes	63	−31.2	19.76		
MEA**				5.50	0.0051
no	101	−24.9	16.46		
yes-FB	20	−38.9	20.63		
yes-OB	12	−25.5	17.50		
Compassionate Use				2.49	0.1167
no	108	−25.9	17.27		
yes	25	−32.1	19.50		
Target population*				3.02	0.0322
0 -| 500	35	−24.2	17.03		
500 -| 3,000	31	−24.8	16.25		
3,000 -| 20,000	33	−24.4	13.88		
> 20,000	34	−34.8	21.40		
Expected Expenditure**				5.15	0.0022
0 -| 15 Mln€	33	−26.2	17.06		
15 Mln€ -| 50 Mln€	35	−25.6	16.95		
50 Mln€ -| 200 Mln€	40	−23.9	14.65		
> 200 Mln€	14	−44.1	24.04		

** Variable significant at 0.01 confidence level.
* Variable significant at 0.05 confidence level.
Legend:
SME: small medium enterprise.
FB: financial-based.
OB: outcome-based.

4. Discussion

The average ΔP is 27.4% (25.1% and 28.6% for orphan and non-orphan drugs respectively).

Table 5
Overview of the multivariate analysis for delta-price.

Source	DF	F Value	Pr > F	R-Square	Adj R-Square
Model	6	4.55	0.0004	0.1917	0.1495
Use of Law N.648/96	1	4.01	0.0476		
MEA	2	2.83	0.0632		
Expected Expenditure	3	4.21	0.0073		

Table 6
Estimated parameters of the final multivariate model for delta-price.

Parameter	Estimate	St. Error	t Value	Pr > |t|
Intercept**	−26.2	2.99	−8.77	<.0001
Use of Law N.648/96				
no	–	.	.	.
yes*	11.9	5.95	2.00	0.0476
MEA				
no	–	.	.	.
yes-FB*	−10.3	4.35	−2.36	0.0202
yes-OB	−3.0	5.17	−0.57	0.5671
Expected Expenditure				
0 -| 15 Mln€	–	.	.	.
15 Mln€ -| 50 Mln€	0.8	4.11	0.19	0.8529
50 Mln€ -| 200 Mln€	4.4	3.99	1.10	0.2742
> 200 Mln€*	−14.4	5.61	−2.56	0.0117

* Parameter significant at 0.05 confidence level.
** Parameter significant at 0.01 confidence level.

The ΔP was higher for innovative drugs (-32.2%) than for all drugs on average. This result may be ascribed to a larger mismatch between the perception of value by the industry and AIFA on innovative drugs. Interestingly, all innovative drugs are reimbursed, except one (orphan) drug, whose manufacturer was not willing to negotiate and lower the proposed price.

Our multivariate analysis suggests that the ΔP is lower when the drug was previously included in the list of off label drugs based on the Italian law 648/96. This result may be justified by the circumstance that it is unlikely that the negotiated price is significantly lowered - during the negotiation process - below the price set when the drug was included in list of off label drugs based on the Italian law 648/96. On the other side a higher ΔP was found for drugs approved for a larger population, with an expected higher drug expenditure: intuitively, the larger is the budget impact the higher will be the required ΔP to get the reimbursement status in order to guarantee the overall sustainability of the system. Both the univariate and the multivariate analyses show an important positive correlation between the existence of a financial-based MEA and the ΔP: this was expected since the ΔP depends also on the application of a MEA. MEAs allowed reimbursing a significant portion of new drugs in Italy. It is most likely that without these agreements, the number of reimbursed drugs would have been lower. On the other hand confidential negotiations have raised debate at the international level [25], because of their effects on external price referencing (ERP) [26]. The use of confidential MEAs results into an official referencing price used for ERP much higher than the actual price on the domestic market [27].

Another interesting result coming from the univariate analysis, is the role played by the implementation of a Monitoring Registry. Drugs' Registries are implemented when patients' eligibility criteria to treatments are complex and when there is a higher uncertainty on the drug's effects in real-life. It is likely that a larger ΔP is negotiated in situations of uncertainty and evidence gaps at the time of P&R negotiations [28].

The present study has some limitations. First, we could rely on a limited dataset, made up of 196 drugs, since it was not possible gathering data through AIFA's electronic information system before 2013. Furthermore, given that the dependent variable is the ΔP of reimbursed medicines, all non-reimbursed drugs (i.e. marketed with a free-price) and drugs that are still undergoing P&R negotiation, were not considered, further reducing the dataset. Such limitations in the data pool might have influenced the statistical analysis. Future works, relying on a larger dataset, could highlight if our findings are confirmed.

Second, our analysis regressed ΔP on regulatory variables, whereas P&R negotiation depends on the clinical value of the drug, including the level of unmet medical need and the added therapeutic value. Some regulatory factors are linked with the clinical value (e.g. the appraisal of innovativeness) and its uncertainty (e.g. ad outcome-based MEA) [29]. However, it is likely that the variable used do not fully capture the role of different perceptions on the clinical value by AIFA and the industry. This may explain why the multivariate specified model explains a moderate percentage (15%) of the ΔP variation. Future studies might include clinical data, e.g. what type of studies were used as pivotal to request P&R, how many and which type of uncertainties were still present at the time of P&R negotiation and what type of clinical endpoints were used to assess the efficacy and safety of the drug. These factors could represent important covariates to be included in the multivariate model, in order to improve its explicative potential. However, it could be the case that the analyzed data contain an inherently higher amount of unexplainable variability so that, even adding other relevant variables to the model, the adjusted R-square value would remain quite low (while not affecting the interpretation of significant variables). Despite these limitations, this analysis provides an insight into the determinants of the outcome of a P&R negotiation, that has not been investigated so far to our best knowledge.

Furthermore, our findings have some relevant policy implications. The impact on ERP has been already discussed. However, another, and possibly more important implication, is whether the ΔP is reasonable or not. Since Italy has not adopted a threshold on the incremental cost-effectiveness ratio that could be used as a rationale to explain the ΔP, we may argue on two contingencies. On one hand, AIFA has successfully relied on negotiation and MEA to push companies lowering their price proposals [30]. On the other hand, price reduction could also indicate that pharmaceutical companies are proposing prices that do not fit with their products' value.

Although further data are needed to confirm our empirical findings, this analysis brings light to the P&R negotiation process conducted by AIFA to guarantee access to new costly medicines [31].

5. Conclusions

The present study has covered an important literature gap, investigating the determinants of the difference between the proposed price for new medicines by the pharmaceutical industry and the final price (ΔP) negotiated with the relevant HTA authority [32].

The average ΔP for all new reimbursed drugs from 2013 to 2017 in Italy is 27.4% (25.1% and 28.6% for orphan and non-orphan drugs respectively). The price reduction is higher for innovative drugs (-32.2%).

The possible determinants that influence more the ΔP are: the use of a monitoring Registry, the use of a FB MEA, the target population >20,000 and an expected expenditure >200 Mln €.

The application of financial-based agreements, which often rely on confidential arrangements, was one of the determinants with the higher impact on price reduction.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on

behalf of or reflecting the position of the Italian Medicines Agency (AIFA).

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No funds were received for this paper and no competing interests exist.

Conflict Of Interest

The authors declare that they have no competing interests as defined by the American Society for Clinical Pharmacology and Therapeutics, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.healthpol.2019.03.009.

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