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INNOVATIVE REIMBURSEMENT TOOLS FOR CANCER TREATMENTS. ANALYZING THE FEASIBILITY OF SINGLE PRICE VERSUS INDICATION BASED PRICING IN MULTI-INDICATION PRODUCTS. THE CASE OF SPAIN

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Executive Summary

The increase in pharmaceutical spending and more specifically in pharmaceutical spending in hospitals is a growing concern for policy makers. The main determinant of this increase is the adoption of healthcare technology, with innovative pharmaceutical treatments accounting for a significant part of this increase in spending, and among these, cancer treatments being of the most important. At the same time, it is increasingly common to have in the market multi-indication oncology treatments, which do not normally offer the same clinical benefit across indications, and as a consequence, it is not possible to reflect the real value of the medicine under a single cross-indication price, constituting a challenge for pricing and reimbursement responsible agents. The health economics literature and the international experience have explored different approaches to bear this challenge, such as indication based pricing, multi year multi indication agreements, or the use of specific funds. The goal of this report is to analyse the practical feasibility of the implementation in Spain of two of them: indication based pricing (with different listed prices per indication for multi-indication products), or a unique listed price for all of them. We perform this analysis through the composition of a multidisciplinary Expert Panel that met twice during 2021 in directed discussions. By explicit request of the Members in the Expert Panel, this report does not endorse any specific recommendation for one or another alternative but just make an analysis of advantages and disadvantages of each system.

The alternative of a unique single price for all the indications of a product is in principle easier to manage, and in terms of regulation, it would not need major modifications to be operative and reduces the risk of arbitrage. However, it moves away from the value-based pricing and may result in strategic behaviour in companies that may derive in delay in access for some patients. If pursued, a weighted average taking into account the added therapeutic value and the expected number of patients that could be benefitted per indication is recommended, always avoiding the only use of a price-volume agreement. The price should be revised every time that there is a new indication approved and periodically to check new clinical evidence on the indications as well as possible deviations in the estimation of the demand.

The alternative of indication based pricing (IBP) promotes value-based pricing, through a different price, based on the value evidenced in the economic evaluation exercise to each approved indication, and in the long run, it improves social welfare and provides the right incentives for innovation and a higher degree of competition in markets.

However, its implementation would need some normative modifications, may result in incentives for arbitrage, greater administrative costs in the purchasing and payment process, and also in monitoring and registering the specific use per indication. At the same time, it can produce some reluctance to the change in local and regional providers and payers who are already negotiating (and should continue to do so) indication-specific discounts. As in the case of single price, prices under IBP should also be revised periodically.

Both alternatives may admit exceptions in order to improve their results. IBP is unfeasible for agnostic tumours or when the administration of the medicine is not independent by indications. Single price is problematic when differences in added value may derive in lack of incentives for commercialization of a new indication, with the loss of access to the medicine for affected patients.

Interestingly, both alternatives share some common challenges for the appropriate implementation. They both rely on the existence of regulation promoting systematic, rapid and homogeneous economic evaluations or at least the characterization of the therapeutic value for all innovative products and all the new indications of them and periodic revisions, and on the existence of a structure capable of performing in a timely manner. That is a major challenge in Spain, where economic evaluation has not yet been implemented in a precise, sophisticated and transparent manner (in the simpler situation of only one listed price per product). It will become much more complicated in the case of indication specific economic evaluations. REvalMed is a new network launched in 2020 by the Ministry of Health to solve this gap, with the goal of adding economic evaluation to therapeutic positioning reports (IPTs). However, it is still too early to determine its success with a low number of economic evaluations published so far.

Another common challenge shared by both alternatives is the need of a Registry of Clinical Data, which should include specific and as complete as possible information regarding the indication for which the product is purchased, and monitor its use for patients per indication, the added value and health outcomes obtained, or adverse effects. That registry should help to the development of economic evaluations to set and revise prices, to identify any deviation from the expected volume in previous budget impact analysis, or to update assessment of added value with new clinical information. That registry should be as homogeneous as possible for all Autonomous Communities. The initial investment for composing that registry may be costly. The question of whether the cost of this registration should be shared between the companies and the regulator

or the provider, or whether it should be borne entirely by one of these parties, is a matter to be debated. Furthermore, the main goal of that registry should be its use for improving clinical benefits for patients and not for price setting (also). If the main objective were price setting, this could increase resistance to the implementation of this register from various stakeholders at the local and regional level, as they already negotiate prices.

In order to attain an appropriate implementation of any of the two alternatives, Spain should provide a regulatory and structural framework in which a registry of clinical data be operative and help the performance of systematic, rapid and homogeneous economic evaluation exercises for all new indications in order to help in their price setting, and periodically, in their revisions. Both alternatives could be used together with other complementary methodologies such as budget impact analysis, the analysis of the degree of competition at the different indications, or even multi criteria decision analysis or cancer specific funds that have hardly been presented in this report.

1. Introduction

1.1. Pharmaceutical spending and cancer spending

In recent decades, the increase in pharmaceutical spending has been a constant concern for the governments of different countries, as spending on pharmaceutical provision is one of the most important components of total public health spending. In Spain, in 2018, expenditure on pharmaceutical provision in hospitals accounted for 6,893 million euros and on pharmaceuticals and medical devices per prescription or dispensing order for 11,063 million euros[1], for a total of 17,956 million euros, which supposes about 24% of public health expenditure (71,145 million euros, equivalent to 5.9% of GDP) (AiREF, 2020).

Pharmaceutical expenditure can be divided into pharmaceutical expenditure through prescriptions dispensed at pharmacies and hospital pharmaceutical expenditure. With regard to the former, the data provided by the OECD Statistics[2] allows us to compare the evolution of this expenditure in different countries. The increase in this type of pharmaceutical spending depends indirectly on the economic cycle in the different countries (see Figure 1), because when the economic cycle affects public accounts, governments take measures that are usually aimed at reducing public spending such as health spending. Thus, the most significant increases in the last twenty years occurred in the years of the 2000s prior to the economic crisis that began in 2008. Since that year, and especially starting in 2009, there has been a notable fall in pharmaceutical spending in countries such as Spain, Italy or Portugal. In the case of Spain, the level of per capita pharmaceutical spending reached in 2009 (US$ 473.7 adjusted for purchasing power parity) fell in the following years and did not return to that level until 2016 (US$ 499.8 adjusted for purchasing power parity).

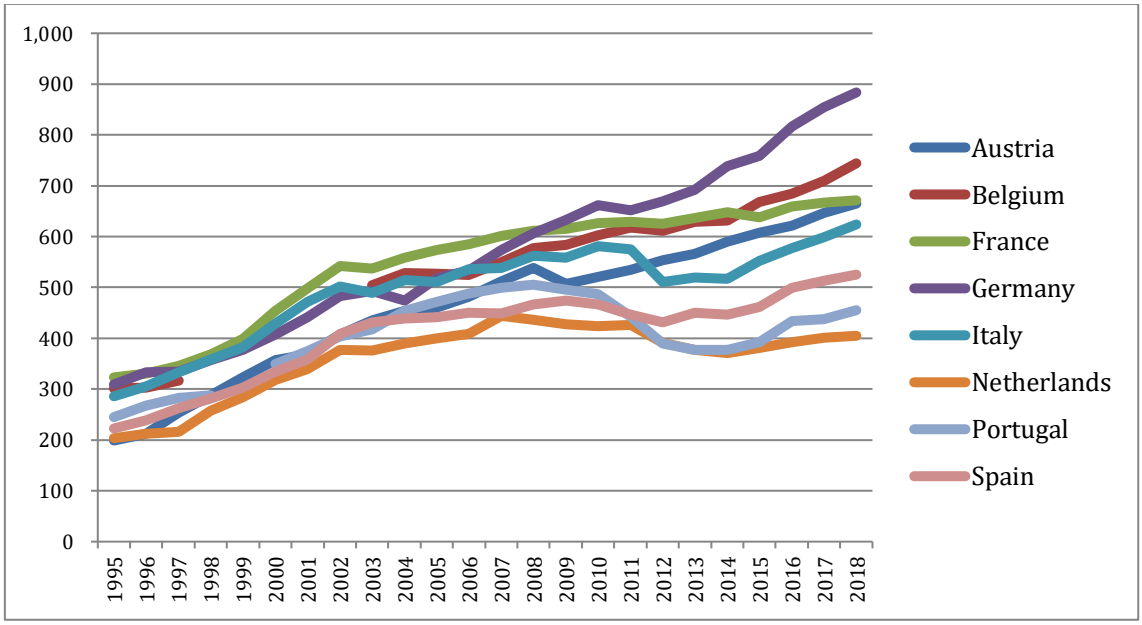
Although pharmaceutical spending through prescriptions dispensed in pharmacies is of great interest, it is important to bear in mind that pharmaceutical spending on oncology treatment, the focus of this report, is concentrated in hospital consumption. For this

[1] Data available at *Ministerio de Hacienda y Función Pública* at: https://www.hacienda.gob.es/es-ES/CDI/Paginas/EstabilidadPresupuestaria/InformacionAAPPs/Indicadores-sobre-Gasto-Farmac%C3%A9utico-y-Sanitario.aspx

[2] Available at: https://stats.oecd.org

reason, we observe the evolution of hospital drug spending in Spain and its relative weight in total drug spending.

Figure 1: Evolution of pharmaceutical expenditure (prescription and OTC drugs) and other non-durable medical products, per capita, purchasing power parities in US$ (current prices, current PPPs)



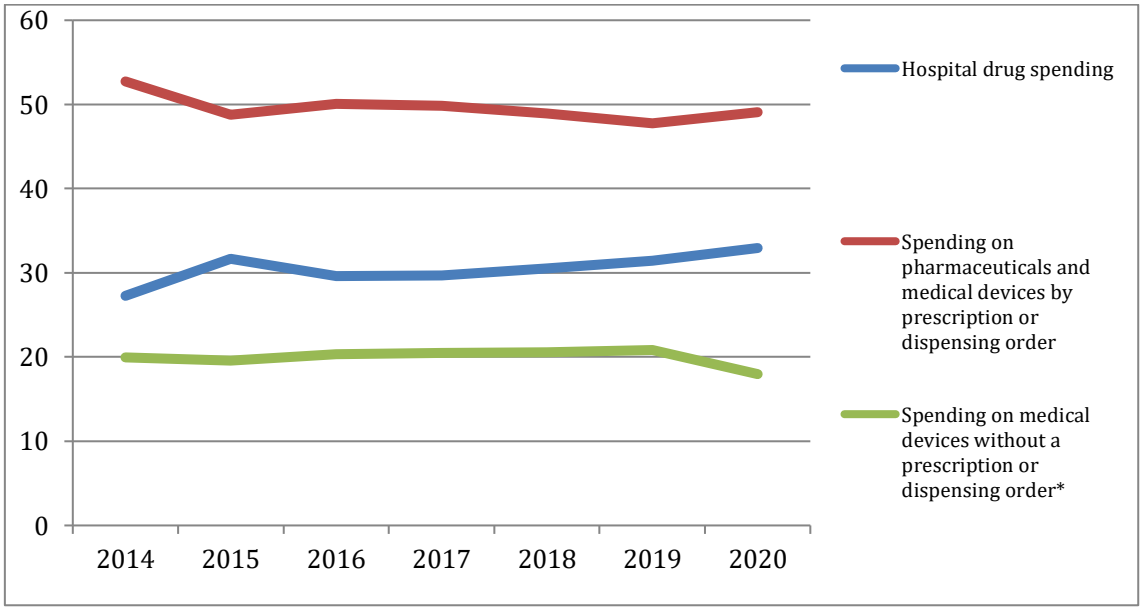
Source: Own elaboration with data from OECD Health Statistics (2020).

Hospital drug spending in Spain stood at 7,877 million euros in 2020 (taking into account the cumulative spending of all public administrations, both the State and the Autonomous Communities), and has experienced significant growth over the last few years, as in 2014 it stood at 5,150 million euros[3]. Thus, in just six years, hospital pharmaceutical spending has grown by 52.95%. Because hospital drug spending is increasing more than other types of drug spending, the relative weight of hospital drug spending is growing with respect to total drug spending (figure 2).

[3] Data available at *Ministerio de Hacienda y Función Pública* at: https://www.hacienda.gob.es/es-ES/CDI/Paginas/EstabilidadPresupuestaria/InformacionAAPPs/Indicadores-sobre-Gasto-Farmac%C3%A9utico-y-Sanitario.aspx

At the same time, it is useful to take into account that health spending is the product of quantities and prices, and so, it is recommended to look at the evolution of prices of hospital drug spending. The Ministry of Health (*Ministerio de Sanidad*) through the *Nomenclátor oficial de la prestación farmacéutica del SNS* shows how the average industrial price (laboratory sales price) of products dispensed in pharmacy has increased from 15.4 euros in 2014 to 20.1 in 2018 (30.5%), while average industrial price for treatments dispensed in hospitals increased more sharply from 211.5 euros in 2012 to 331 euros in 2018 (56.5%) (Ministerio de Sanidad, 2021a). It is important to note that the methodology used in these calculations for average industrial prices and the concept of units that is used is not explicitly stated.

Figure 2: Relative weight of the different components of pharmaceutical spending in Spain from 2014 to 2020.



Source: Prepared by the authors with data from the Ministry of Finance and Public Administration.

* The figure for 2020 corresponds to the series in which COVID products have been excluded.

Analysing the hospital drug consumption by therapeutic subgroups (at level ATC2), we observe how in Spain in 2018, Antineoplastic Agents (L01) was the subgroup with the highest consumption, with 1,748 million euros, supposing approximately 23.9% of total hospital spending in drugs (Ministerio de Sanidad, 2021b).

As a consequence, hospital drug spending in general, and innovative oncology treatments are an important concern for health policy makers.

Because of this concern, the health economics literature has extensively analysed this topic in the last decades. Newhouse (1992) found that the main determinant of growth in health spending is the adoption of health technologies, of which new medicines form part. More recent work by Willeme and Dumont (2015) reached the same result. Precisely that is the case of the spending on oncology treatments, with highly innovative but costly products. The health economics literature has also evidenced how innovative medicines have a large positive social impact through an increase in life expectancy (Cutler et al., 2006; Lichtenberg 2014, 2016), improving patients' quality of life (Scherer, 2000; Lichtenberg and Virabhak, 2007) or reducing avoidable mortality or the presence of physical or cognitive limitations (Lichtenberg and Virabhak, 2007). At the same time, innovative medicines have also changed the way in which healthcare is provided between hospitals and outpatient care (Lichtenberg, 2019). As a consequence, the undoubted benefits derived from innovative medicines are accompanied by an increase in expenditure that makes it necessary to pay attention to them (García-Goñi, 2022).

In the specific case of oncology, it is estimated than the cost of cancer accounts for up to 30% of total hospital expenditure across Europe (Simoens et al., 2017) and it is expected that spending in oncology will continue to dominate spending on medicines, especially in high income countries (Waters and Urquhart, 2019; IQVIA, 2018).

1.2. The adoption of innovative products in a sustainable health system

Because of the undoubted benefits derived from the use of innovative pharmaceutical products in general, but specifically in oncology treatments, the health economics literature recommends the use of economic evaluation through the analysis of both, incremental costs and benefits derived from the use of the innovative product with respect to its best alternative available. Many countries, through different schemes, have implemented at least at some extent, economic evaluation exercises in the decision of financing treatments within their health systems.

It is important to note that the typical economic evaluation exercise implies the comparison of the treatment with its best available alternative or standard of care, and it is assumed that this exercise is valid for one indication. That way, the economic evaluation can be used to set the reimbursement price of the new treatment based on

the therapeutic value added, or to correct prices when they have been set in an early stage to accelerate their approval and authorization so as to improve access of patients to medicines. For instance, Lauenroth et al. (2020), with data from Germany, found that after evaluation, reimbursement prices for new oncology medicines decreased.

Godman et al. (2021) review different approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and their implications. In particular, they explain the advantages and disadvantages of minimum effectiveness criteria, Managed Entry Agreements, Multi Criteria Decision Analysis, Differential/tiered pricing including multi-indication pricing, or fair and transparent pricing models, being the most relevant MEAs, MCDA and multi indication pricing. With respect to Managed Entry Agreements (MEA), they can be divided into financial-based schemes, usually with confidential rebates, discounts, or price volume agreements; and performance or outcomes-based schemes, with some outcome guarantee schemes or agreed prices based on agreed outcomes. A recent OECD report (OECD, 2020) suggests that MEAs should be improved by supporting the generation of real-life clinical data in order to reduce the uncertainty regarding the effectiveness and safety of new oncology medicines in routine clinical care, given that many times, those treatments are launched with immature data. With respect to Multi Criteria Decision Analysis (MCDA), MCDA is a methodology that allows providing the ranking of priorities among different programs, by inferring preferences of the respondents among different attributes. Hence, it provides a rationale to simplify complexity in the health policy decision-making process. Although several public agencies and health insurers are already using or proposing the MCDA approach (Godman et al., 2021) for new medicines, there are concerns that quantitative MCDA approaches may not be lead to good quality recommendations (DiStefano and Krubiner, 2021). With respect to the multi indication pricing or indication based pricing (IBP), there is a growing debate regarding its advantages and they will be the focus of this research project, specifically for the case of its implementation in Spain.

1.3. Multi-indication in new cancer treatments

Marketing of new and existing medicines with new indications used alone or in combination is increasing and it is expected that this trend of increasing presence of multi-indication treatments in the market will continue in the future, especially in oncology (Campillo-Artero et al., 2020). Hence, it is increasingly common to have in the market, specifically in oncology, multi-indication treatments, that can be used for patients

suffering different conditions, diseases or stages of the disease. In fact, by 2014, approximately half of oncology medicines were effective in more than one indication and by 2020, this rate had reached over 75% (Lawlor et al., 2021; IQVIA, 2019).

In the case of multi indication medicines, it is important to take into account that the value of a molecule may be substantially different when it is used for different indications because of differences in clinical benefits or in the health burden or level of unmet needs per indication, and it also matters whether it is used alone or in combination with other therapies (Mestre-Ferrándiz et al., 2018). Those differences, in principle, should be reflected in the price as well as the social or individual willingness to pay for the different indications of the treatment under different health systems (Campillo-Artero et al., 2020). Multi-indication pricing, or Indication Based Pricing (IBP) consists of charging a different price for each indication (Mestre-Ferrándiz et al., 2018) with the goal of differentially cover the R&D investment based on the incremental clinical benefit or the cost-effectiveness ratio of each indication (Campillo-Artero et al., 2020).

Campillo-Artero et al. (2020) provide a systematic review of the literature dealing with multi-indication pricing models. They find that there are three different approaches or models for the IBP implementation: the use of different brands with different prices for the same medicine, the use of a single price calculated as an average for the various indications, and the use of a single price with differential discounts. Campillo-Artero et al. summarize the pros and cons of the three alternatives, and do not find practical applications of pure IBP, but they point to single pricing for medicines as the most prevalent approach.

Because the focus of this research project is to analyse whether a system of IBP is feasible in Spain, and its pros and cons, we will be using below the learnings from previous analysis of this topic such as, among others, Campillo-Artero et al. (2020), Mestre-Ferrándiz et al. (2018), or Lawlor et al. (2021).

2. Context of the research project and methodology

2.1. The Expert Panel

In a context in which multi-indication is increasingly common for cancer treatments, the goal of this research project is to analyse the feasibility of implementation of different

options out of those introduced in the health economics literature, so as to accelerate the access to innovative oncological treatments to patients but taking into account the need of promoting the sustainability of the National Health System in Spain.

To this end, first, an Expert Panel was first established. The number of members of the expert panel was of ten (nine plus de coordinator and principal investigator of the research project). The composition of the Panel of Experts took into account the need of experts with different background. In order to guarantee a multidisciplinary character of the panel, different profiles are represented, as patients, health economists, public officers with experience in buying oncological treatments for the provision within the National Health System, clinicians, and responsible for cancer strategy in Spain.

The Expert Panel was composed by:

Patient perspective:

- Begoña Barragán. President, Spanish Group of Cancer Patients (GEPAC, *Grupo Español de Pacientes Con Cáncer*).

Cancer Strategy:

- Josep María Borrás. Coordinator, Cancer Strategy of the National Health System

Public officers with regional responsibility in pharmaceutical policy or with payer experience:

- José Manuel Ventura. General Director of Pharmacy and Medical Devices, Autonomous Community of Valencia.
- Antoni Gilabert Perramon. Director of Innovation and Partnership, Catalan Health and Social Care Consortium
- Marta Roig Izquierdo. Coordinator, Medicine Managed Access, CatSalut, (Catalan Health Service).

Clinical perspective:

- Ruth Vera. Chief of Medical Oncology Service, Navarra Hospital Complex (Pamplona).

Industry perspective:

- Pedro Luis Sánchez. Director, Economic Studies Department at Farmaindustria.

Health Economics:

- Félix Lobo. Emeritus Professor, Universidad Carlos III de Madrid.
- Jaime Espín. Professor, Andalusian School of Public Health.
- Manuel García Goñi, Professor of Health Economics, Complutense University of Madrid (Principal Investigator)

It is important to mention that even in the case of Experts with responsibility at the hospital or regional levels, they were asked to provide insight from their experience that could be used at the national level in Spain.

The Expert Panel met twice in March and in June 2021. Both were virtual meetings and most members could participate in them. For those Experts who could not participate in the meetings, the principal investigator was in touch with them for receiving further comments either by email or by phone conversations. Previously to each of the meetings, the participants received the agenda of the meeting with the expected topics to be discussed.

2.2. Setting the goals and scope of the research Project

There are different approaches that have been analysed in the health economics literature to meet the challenge of increasing pharmaceutical spending on multi-indication oncology products. Out of all the different approaches, we focus our analysis into two options:

- A unique listed price for all indications of the same product

- Indication Based Pricing (listed prices) for multi-indication products

The goal of this project, as presented to the Members in the Expert Panel, is to provide some practical view about the feasibility of implementing Indication Based Pricing or a unique listed price for all indications in the case of multi-indication treatments, with the focus of oncology treatments, in Spain. It is important to note that the perspective undertaken for the Expert Panel is to provide the advantages and disadvantages of both of the options, without any intention of endorsing one or the other. As a consequence, this report is intended to be neutral between the two options and to serve as a decision tool for the decision-maker.

2.3. Consensus and lack of consensus

2.3.1. Accelerating access an delay in access to innovative medicines

The Expert Panel agrees on the desirability of accelerating access of innovative cancer treatments to patients who suffer from different indications and can benefit from the authorization and financing of these specific drug indications, but always bearing in mind the ultimate goal of the sustainability of the National Health System. As a consequence, once a new innovative product (or a new indication for a previously authorized product) is authorized by the European Medicines Agency (EMA), the time it takes until it is approved for use and financing in Spain should be minimized, provided that a series of conditions imposed are met. In other words, it must be taken into account that not all approved products or indications present the same level of urgency to try to accelerate their financing and access to patients. We discuss below (in the subsection setting the price) regarding the set of conditions imposed in order to accelerate the process of pricing and thus, financing and access.

With respect to the accelerated access to innovative medicines, EFPIA publishes annually the "Patients W.A.I.T. Indicator" (the last one published in May 2021 referring to 2020) (EFPIA, 2021). This publishes statistics on the number of days of delay until a product is marketed since authorization by the EMA. In the case of Spain, it is 413 days, which seems to be high and has increased in the last years. However, the Expert Panel did not reach a consensus relative to the interpretation of this delay. The reason is that in the mentioned statistic, there is a missing piece of information, relative to the time at which the company applied to the different States for financing. Thus, it is not clear what percentage of the delay depends on the company or the payer. At the same time, the

application of the international reference price system, and the influence that pricing in one country has on pricing in other countries, means that companies sometimes prefer to obtain higher prices in other countries in advance of the price in Spain.

Setting the price

In this report, we discuss about setting prices for multi-indication treatments, either one for all the different authorized indications of a medicine, or one price per indication. The Expert Panel agrees that the setting price that we discuss here is the listed price of the medicine, which is the maximum price that could be legally paid for that medicine in Spain. That maximum (listed) price is set by the Interministerial Drug Pricing Commission (*Comisión Interministerial de Precios de los Medicamentos*, CIPM). As a consequence, this report can be used as a tool for the CIPM in setting listed prices.

It is important to take into account that the listed price for a medicine (or for each indication if we had Indication Based Pricing) is different to the actual cost of the product or the price that is actually paid by the payer (discounted price). The reason is that in Spain, in the case of medicines for hospital use and dispensing, the price that is actually paid by the payer (discounted) is negotiated by the purchaser/payer in agreements at the micro level. This report does not discuss about the ways of setting the discounted price at the micro level. In contrast, in the case of drugs dispensed in pharmacies (approximately half of total pharmaceutical spending), there is no room for such negotiation. Because of the high concentration of pharmaceutical spending in the hospital for oncology treatments, negotiations for discounts off the listed price are relevant to this report.

The concept of value of the medicine and its relationship with the price set within, for instance, a value based pricing strategy, is commonly discussed. The Expert Panel notes that the concept of value should consider not only the pharmacological treatment but also, ideally, the entire process of providing care, which includes the action of doctors, nurses, or in general other health providers, and the intervention of all health technology in for instance, the diagnosis stage. Without the right intervention of health providers or health technology, the added value of the medicines would decrease. For that reason, to the challenge of setting the value and the price of the medicine, it is added the difficulty, which this study does not address, of dividing or distributing the value created among all the participants in the care provision process.

With respect to the model for setting a single price or different prices per indication, there is consensus within the panel of experts that different criteria should be taken into account, such as economic evaluation, budget impact, or the level of competition in the relevant market.

Economic evaluation

The health economics literature (see for instance Drummond et al., 1997) shows how governments or health insurers try to influence the price and utilization of medicines to encourage efficiency in the use of resources. Economic evaluation represents a relevant tool in order to attain that goal because through its exercise, it provides an estimation regarding the value added by each new product or new indication with respect to the treatment available in the market.

The Expert Panel agrees that the model of setting prices for medicines (no matter whether it is one per product or per indication), in general, should include an independent economic evaluation exercise.

It is important to note that Spanish regulation already mandates the use of economic evaluation in article 94 of the Royal Legislative Decree 1/2015, of July 24, 2015, approving the revised text of the Law on guarantees and rational use of medicines and health products:

> "The Interministerial Drug Pricing Commission (*Comisión Interministerial de Precios de los Medicamentos*, CIPM) will take into consideration the cost-effectiveness and budgetary impact analyses".

However, even if the economic evaluation exercise should always be included in the process of setting prices, regulation is quite vague, as it does not specify how that exercise should be designed.

With respect to the content and format of the economic evaluation exercise, the Expert Panel recommends that it should be designed so as to estimate the incremental clinical benefit of the innovative treatment for each authorized indication, it should be relevant, and if possible, it should be measured in quality of life. That analysis could result in a

classification of innovative products by added value in each indication. Thus, a multi-indication product might become very innovative for one indication but not as innovative in other indications. That level of innovativeness and value added in each relevant market should be taken into account.

With respect to the analysis of the costs, the economic evaluation exercise should consider the length of inpatient stays in hospitals, as well as the type of hospital. It is important to note that hospitals of different degree of complexity present different structure of costs. At the same time, it is recommended to consider the cost of the entire process instead of only the costs of the pharmacological treatment. As discussed above, the value of the innovation relies on the intervention of different agents who assume different costs that should be taken, if possible, into account.

At the same time, the Expert Panel finds that there should be regulation approved regarding the required content and design of the economic evaluation exercise in the form of clear and transparent guidelines, so that to the extent possible, all the economic evaluation exercises are homogeneous (and comparable). It is a common complaint for payers to find economic evaluation exercises (from different companies and different products) of very different nature, with different design and difficult to be compared. While it is perfectly understandable that each product, or each indication of a product may have their own specificities and as a consequence, there may be different nuances in the presentation of the results and in the focus of the exercise, from the point of view of the decision maker it would be much easier if there was a specific format to be followed in order to better understand the added value of the medicines in their respective indications.

At the same time, transparent guidelines on the economic evaluation would reduce the level of uncertainty suffered by companies in the innovator industry, since they would have a better knowledge of the key variables to be presented and taken into account in price setting (either per product or per indication).

Vague regulation regarding the way in which economic evaluation exercises are presented, results into a higher degree of distrust between the industry and the administration, which in turn could delay pricing and financing decisions. Also, with respect to the rule of decision in the economic evaluation analysis, it is important to take into account that the discounted price that is actually paid by the payer may present significant differences with respect to the willingness to pay.

It is out of the scope of this report to provide such format and content but that is a task that remains to be performed and approved either by the Ministry of Health or by an independent body or Agency in charge of them. In fact, a reform in this direction has already started its implementation. The Standing Committee on Pharmacy of the Interterritorial Council of the National Health System (*Comisión Permanente de Farmacia del Consejo Interterritorial del SNS*) approved in July 2020 a "Standard Operating Procedure for clinical evaluation, economic evaluation and therapeutic positioning for the drafting of therapeutic positioning reports for medicines in the Spanish NHS" (*Procedimiento Normalizado de Trabajo de evaluación clínica, evaluación económica y posicionamiento terapéutico para la redacción de informes de posicionamiento terapéutico de medicamentos en el SNS*). The published text includes a template in Annex 1 for the first phase of the procedure, although that template can be changed depending on the needs of each situation or indication. Then, in October 2020 the REvalMed Coordination Group was constituted as a therapeutic evaluation group, an economic evaluation group and seven evaluation nodes by clinical areas that will act as expert reviewers appointed by the Autonomous Communities. The key of this reform is the mandatory inclusion of economic evaluation exercises in the therapeutic positioning reports (IPTs, *Informes de Posicionamiento Terapéutico*), to provide information before the decision on the price and financing of the medicine for better decision making from the moment of its adoption. Currently, at least 13 of the reports that REvalMed is performing include economic evaluation. The first published IPT including economic evaluation following the draft was published on 25 June 2021[4].

Although this reform is going in the right direction, it is still too early to establish whether it will be successful, or whether the structure created to perform the economic evaluations and include them in the therapeutic positioning reports will be sufficient and capable of carrying out the reports in an agile manner. In any case, it is a necessary starting point. At the same time, while there is consensus about the need of performing and including economic evaluation in the process of setting prices, it is not clear for all the Members of the Expert Panel whether the economic evaluation exercise should be

[4] Therapeutic Positioning Report of talazoparib (Talzenna®) in patients with HER-2 negative breast cancer with BRCA 1/2 mutations in progression to previous treatments (*Informe de Posicionamiento Terapéutico de talazoparib (Talzenna®) en pacientes con cáncer de mama HER-2 negativo con mutaciones BRCA 1/2 en progresión a tratamientos previos*). Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2021/IPT_32-2021-Talzenna.pdf?x60265

included in the same document together with the therapeutic positioning report, or whether, being both necessary, they should be dealt with independently in different documents of the process.

Finally, and that has also noticed in the health economics literature (Drummond et al., 1997), evaluation cannot be used as the only tool to set the price for a medicine or for each of its indications. Other attributes should also be taken into account in the decision, since it is necessary to decide how to share the added value and welfare created by the innovative product between the society and the innovating company that expects to be compensated for its innovative effort. The Expert Panel agrees that besides economic evaluation, other attributes should be taken into account in setting prices for new products or new indications of existing products, as it is already stated in the Spanish regulation.

Budget impact

A budget impact analysis (BIA) estimates financial consequences of adopting a new health technology or intervention given its specific health context (Trueman et al., 2001; Mauskopf et al., 2007; Sullivan et al., 2014). A budget impact analysis is usually performed in addition to a cost-effectiveness analysis when submitting evidence to support national or local formulary approval or reimbursement (Orlewska and Gulacsi, 2009). In fact, the economic evaluation exercise and the budget impact analysis are complements because the former evaluates whether an intervention provides value relative to an existing intervention (with value defined as cost relative to health outcome) and the second evaluates whether the high-value intervention is affordable.

In order to set the price for a product or for its different authorized indications, it is necessary for the payer to take into account the impact that the new indication is going to have in the public budget. For that reason, it is important to collect information on estimated volumes of the demand, given by the number of patients that would be in optimal conditions to benefit from that product, per authorized indication. The need of a high quality registry of patients per indication is a must.

A budget impact analysis is estimated by taking the expected cost (listed price) of an intervention or the innovative oncological treatment for the analysed indication, and multiplies it by the expected demand, given by the number of patients, taking into account

the approved clinical guidelines, that would be affected by the presence of that treatment in the market. As in the case of economic evaluation, when developing a budget impact analysis, it is necessary to consider that the innovative treatment in the indication may replace the existing standard of care (substitution), may be used in addition to the existing standard of care (combination), or may be used only in situations where there was no existing care (due to, for instance, patient intolerance of standard care). It is also necessary to conduct sensitivity analysis. What usually differs with respect to the economic evaluation exercise is that the budget impact analysis is often used for resource allocation purposes, and so, it mostly takes the payer's perspective, instead of looking, as many times in cost effectiveness analysis, the society or the provider's perspective.

In order to design the budget impact analysis it is necessary to define whether the listed price is going to be unique for all authorized indications or it is going to be different for each of them. In the case of indication based pricing, the budget impact analysis of each indication would be independent, while in the case of a unique listed price, the budget impact analysis would be composed by the aggregated demand of all indications times the listed price (obviously, if done in this way, discounts would not be considered).

A high budget impact may lead price setters to try to directly lower the price of the product (or indication), or to convene some kind of price-volume agreements or negotiate payment conditions from the payer to the innovative company.

Competition in the market for each indication

The Expert Panel convenes that in order to set the price of a product or for each of its authorized indications, besides the economic evaluation exercise, it is necessary to take into account the degree of competition in the relevant market.

The relevant market for a multi-indication product is defined as the relevant market of each of its authorized indications. It is not the same to get a product authorized for an indication with unmet needs than for an indication in which there is only one other commercialized product, or for an indication in which there are several other products. The structure of the market defines the market power that the company with the recently authorized product for an (or several) indication. That structure of the market needs to be taken into account when setting the price.

Even if the economic evaluation exercise already provides an insight regarding the value added in the market of each indication, the perspective of the market structure provides the degree of competition, which is also taken into account in economic models of setting prices. The industrial organization theory shows how the higher the degree of competition in the market, the closer the price will be to marginal cost and, therefore, the lower the price level. Evidence of this relationship is shown applied to the pharmaceutical industry, for instance, in Wiggins and Maness (2004).

Even if an estimation of the therapeutic added value is provided by the economic evaluation exercise and the expected spending in the medicine by the budget impact analysis, the analysis of the competition per indication may provide important insights of how mature the market of each innovation is, or the degree of unmet needs, and that information could be used in order to set the priorities in the financing of innovative products or new indications for multi-indication products.

Other attributes and methodologies

Multicriteria Decision Analysis (MCDA)

The Expert Panel considers that economic evaluation, budget impact analysis, and the analysis of the degree of competition at each relevant market (indication) are the most important methods to be taken into account in the price setting. However, the Panel also discussed the convenience of analysing other alternatives, to explore other attributes. In that sense, the Expert Panel mentioned the *Multicriteria Decision Analysis (MCDA)* as the candidate methodology to be included into the discussion of the price setting decision, because it is able to consider other attributes.

The reason to add other attributes in the price setting decision different to economic evaluation is that too much emphasis on cost-effectiveness may result in limitations to holistic decision making because it excludes important factors such as innovation, disease severity, size of patient population, equity, or clinical guidelines (Marsh et al., 2014; Drake et al., 2017). At the same time, it may be considered that lack of cost-effectiveness is not a necessary or sufficient condition to reject access to treatments, for instance in the case of indications with unmet needs. However, the use of the MCDA methodology is not without problems or risks, even when all the recommendations of good use guidelines are followed (Thokala et al., 2016; Marsh et al., 2016). Among the

drawbacks are the difficulty of inferring societal preferences through the selection of attributes and levels, the possibility of influence on the results in case of the existence of pressure groups, or the dealing with uncertainty (Puig-Junoy, 2018).

In any case, it is important to note that Spanish regulation includes other items to be taken into account in the pricing and reimbursement procedure in addition to economic evaluation, such as severity of the disease, therapeutic and social value of the drug, existence of therapeutic alternatives, degree of innovation of the drug, etc.[5]

Specific Funds

A different methodology adopted at some countries to ease and accelerate the access of patients to innovative medicines is the use of *Specific Funds*. That is the case of the Cancer Drug Fund (CDF) in the UK, used when an innovative medicine is expected to meet the criteria for routine use in the National Health Service, but there is still too much uncertainty with respect to clinical data (NHS England, 2016). The CDF provides an early funding source, via Interim Funding Agreements (IFA), for treatments that receive a provisional positive recommendation from the NICE, without them having to wait for NICE final guidance to be published, and subsequent entry into the routine commissioning system; and a source of funding, via Managed Access Agreements (MAA), for treatments showing clinical promise but where more data is needed to resolve uncertainty around their effectiveness (Cancer Drugs Fund, 2021).

The NICE provides very specific guidelines with respect to the patients and the comparators allowed and the company prepares the proposal following those guidelines and using all the evidence collected to perform the cost effectiveness analysis. As a result, NICE may recommend funding for the innovative treatment or make the company wait until further evidence is available (Lawlor et al., 2021). If funding is recommended, access is immediate, and the company and NHS England sign a Managed Access Agreement in which it is specified the Data Collection Arrangement –providing details on the outcomes that need to be collected in a given period (usually 2 years) in order to resolve clinical uncertainty -, and the CDF Commercial Agreement –determining the cost of the innovative treatment (Lawlor et al., 2021).

[5] Royal Legislative Decree 1/2015, of July 24, 2015, approving the revised text of the Law on Guarantees and Rational Use of Medicines and Medical Devices, article 92 of Procedure for public financing.

Italy also implemented a specific fund innovative treatments in 2017, with the allocation of €1b, half of it dedicated to oncology treatments. The allocation of those funds is performed following an algorithm assessing the treatment degree of innovativeness medicines, taking into account unmet therapeutic needs, added therapeutic value, and quality of the evidence collected in the clinical trials. The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) classifies the new treatments into innovative, not innovative or conditionally innovative, and those classified as innovative obtain immediate access to funds for a period of 3 years (Lawlor et al., 2021).

The Expert Panel considers that through Specific Funds the regulator could provide a signal to the market about the areas it considers to be priorities for funding, and thus, the regulator would be incentivizing research in the areas of greatest interest or with the greatest funding commitment. As in other countries, this fund could consist of an annual spending ceiling, although it would be necessary to provide transparent guides on how funds would be allocated. It is important to take into account that the use of specific funds setting funding priorities may be considered inequitable, since it implies that treatments are financed in a preferential manner for some patients with certain pathologies compared to others. The use of specific funds has been implemented in Spain, for example in the case of Hepatitis C or the Covid pandemic. In the case of Hepatitis C, it was used due to an exceptional situation with a high degree of social pressure and without following any rational decision-making criteria to decide whether or not it should be a priority (Campillo-Artero et al., 2016). Thus, the use of specific funds, if any, must always be justified.

In any case, and even if the Expert Panel discussed briefly about methodologies such as MCDA or Specific Funds, these alternatives are out of the focus of this report.

Revision of prices

The Expert Panel recommends that the price setting phase does not finish when prices are set (single price or indication based pricing). Instead, it is recommended to provide regulation regarding a procedure to review the price(s) after each new indication authorization, or at least every two years based on the new information available.

With respect to this, Spanish regulation allows for the revision of prices of medicines in article 94 of the Royal Legislative Decree 1/2015, of July 24, 2015, approving the revised text of the Law on guarantees and rational use of medicines and health products:

> "Consideration will be given to return mechanisms (linear discounts, price revision) for innovative medicines".

And much more directly, in article 96 of the same Royal Legislative Decree 1/2015:

> "1. The price fixed in accordance with the provisions of Article 94 shall be reviewable ex officio or at the request of a party in accordance with the provisions of Articles 102 and following of Law 30/1992, of November 26, 1992, on the Legal Regime of the Public Administrations and the Common Administrative Procedure.
>
> 2. Apart from the cases foreseen in the previous section, the price of a medicine may be modified when required by changes in the economic, technical or sanitary circumstances or in the assessment of its therapeutic usefulness.
> …".

Even if the regulation allows for a price revision, there is a lack of automatic mechanism that revises prices. And in the case of multi indication medicines, this revision should take place every time that there is a new indication approved for the medicine.

The main reason for this is to avoid the possibility of strategic behaviour by innovative companies that could eventually promote the entry in the market (asking for authorization and financing) of indications with higher added value and delaying the commercialization (delaying their submission for authorization or financing) of lower added value indications.

It is important to note that the revision of prices could be upward or downward, always depending on the result provided by the formula used, and the new competition that exists in the indication(s).

2.4. The discussed alternatives

The scope of this report is the analysis of feasibility of two alternatives:

- a single listed price for all indications of the multi-indication product (or product-based pricing), and
- Indication specific listed prices (or indication specific discounts).

3. First Alternative: Product-based pricing

3.1. Background

The health economics literature has reviewed in different papers the option of a product based price for the medicine no matter the number of indications that are approved (see for instance Persson and Norlin, 2018; Mestre-Ferrándiz et al., 2018; Campillo-Artero et al., 2020; or Lawlor et al., 2021). When the price and reimbursement strategies consist of one single price (product-based pricing), it is not possible to solve the trade-off between the goals of access for the different (authorized) indications and efficiency and cost control. The reason is that if price were based on that of an indication for which the added value is high, then that price could be too high, be left out of financing, and leave without access to the medicine to patients suffering indications for which the medicine provides less value. Differently, if price were based on that of an indication for which the added value is low, then innovative companies would see reduced their incentives to apply for approval and financing of the product for indications for which the added value is greater, and in the long run, at some extent, to invest in Research & Development.

A different complication happens when the medicine is used in some indications in combination with other medicines compared to when used as monotherapy. In such cases, it may be difficult to estimate the added value provided by each product to the combination, especially when the products in the combination are innovative and expensive when used in monotherapy (Persson and Nolin, 2018), which would significantly increase the price of such combination.

"Blended single price" or "weighted-average" approaches

Campillo-Artero et al. (2020) in their review, find that different health systems include different "blended single price" or "weighted-average" approaches. The simplest would consist of a single price calculated as an average across indications and weighted solely by expected volumes of use for each indication. That simple model would not incorporate

value in the weighting but only the potential number of patients per indication, in order to determine the budget impact of the medicine and the economies of scale in its production process with high fixed R&D costs. A most complex approach would consist of the use of added therapeutic value of each indication in the formulae for the weighting average. France, Germany or Australia would constitute examples of weighted average approach (Mestre-Ferrándiz et al., 2015; Persson and Nolin, 2018). In France, clinical benefit and incremental clinical benefit ratings are granted for each indication separately, as also clinical comparators and target population size. The pricing committee defines an average price that represents the value across indications weighted by the expected volume (Flume et al., 2016). In Germany, the evaluation of added clinical benefit is performed at the indication level, with specific comparators per indication, and the expected demand per indication is taken into account (Mestre-Ferrándiz et al., 2018). Once an indication is approved, access to the medicine for patients of that indication is immediate and reimbursement is set at the official list of launched products for up to 1 year following their approval, and the manufacturer is allowed free pricing during this time. After that period, new indications are evaluated by the centralised AMNOG P&R process resulting in renegotiation of the existing reimbursement price (Lawlor et al., 2021).

Multi-year-multi-indication (MYMI) agreements

A different approach is constituted by Multi-year-multi-indication (MYMI) agreements. MYMI agreements group different indications in the same agreement and last several years. The goal of MYMI agreements is to accelerate patient access for upcoming indication, reduce uncertainty and improve predictability for payers and companies with respect to prices. Hence, prices are no renegotiated after each new indication is approved (Lawlor et al., 2021). Under MYMI agreements, clinicians can immediately prescribe the medicine right after the approval of the different indications. Lawlor et al. (2021) explains how MYMI agreements may incorporate different components, such as a pricing arrangement that covers upcoming indications, an abbreviated upfront value assessment or no assessment for new indications, pre-launch agreement to reimburse new indications over a specific period, or budget allocation.

Belgium and the Netherlands are the most significant examples of countries using MYMI agreements. In the case of the Netherlands, there is an agreement per product, the agreement is confidential and is revised annually, although it is understood that they are of the form of a price-volume agreement. With this type of agreements, approved

indications do not need to go into the normal HTA assessment, although it is required to obtain a positive recommendation by the oncology appraisal committee to be reimbursed (Lawlor et al., 2021).

The Spanish context

In the Spanish context, product based price, or a single listed price for the medicine, regardless of the number of indications that have been authorized for that medicine, implies to set the maximum price to be paid in all national territory. In fact, this alternative is a continuist alternative because, in reality, there is currently only one list price per medicine. In practice, what happens on numerous occasions is that when a new indication for a medicine is authorized, the price is usually revised downward because the expected volume of use of the medicine increases. As a consequence, the discussion here, from the point of view of the Expert Panel, is more about how to set that single listed price and how it should be revised afterwards, using economic evaluation, once new indications are authorized and approved for financing.

3.2. Mechanics of the alternative

As mentioned above, currently there is only one price per product, and therefore, there is no need to change the current system and regulation to maintain that.

However, if the Interministerial Drug Pricing Commission (CIMP), in charge of setting the listed price of medicines, decided to promote a single price specifically for multi indication oncology treatments, the Expert Panel would recommend to implement a model following the weighted-average approach. In that model, ideally, the listed price would be set taking into account the added therapeutic value of each approved indication for which funding is authorized, as well as the expected number of patients that could be benefitted, also from each indication (and would not be a weighted average that took into account only volumes, as in a price-volume agreement). It is important to note, in any case, that this listed price does not necessarily match the price paid for the product. In the Spanish context, there is flexibility that allows negotiation between payer and companies. That flexibility and negotiations between payer and companies should still be in place and maybe result in discounts that might be indication specific, depending on the last data received from clinical trials.

Assessment of value

The weighted average, as mentioned, should include economic evaluation exercises per each indication of the product. In those economic evaluation exercises, as usual, it is very important to assess the clinical benefits and costs of the innovative product per indication or relevant market. We have mentioned above that clinical benefits should be measured taking into account quality of life. Also, there are concerns in the use of willingness to pay in order to set prices of innovative products. It is important to note that value based pricing does not mean to set a price representing the maximum willingness-to-pay threshold. As Campillo-Artero et al. (2020) explains, if the price is equal to the maximum willingness-to-pay threshold, this does not mean that this price is appropriate but that it represents a maximum price, in which the company (monopolist) is maximizing profits and capturing all consumer surplus. In this sense, it is important to point out that willingness to pay is not the only thing that must be taken into account in price setting to prevent the entire consumer surplus from ending up in the pockets of producers. Also, in the case of multi indication treatments, it is important to take into account that the added value at each indication might depend on the market structure and level of unmet needs at each of them, affecting the willingness to pay.

With respect to the assessment of the value it is proposed to analyse the use, as an alternative, of the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)[6] which was launched by the European Society for Medical Oncology (ESMO) to facilitate improved decision-making regarding the value of anti-cancer therapies, promote the accessibility and reduce inequity of access to high value cancer treatments (ESMO, 2021), as it was developed as a validated and reproducible scale that is applicable across the full range of solid tumours in oncology (ESMO, 2021).

As mentioned above, it is very important in the Spanish context not only to generalize the use of economic evaluation as one of the elements to take into account for in the price setting, included or not in the therapeutic positioning reports, but also the format and content of that exercise with the objective of shortening the time required for its review, and the reduce the uncertainty regarding what is needed for the company, and the distrust about the interpretation of the results for the payer. The current modification of the therapeutic positioning reports including economic evaluations covers, in principle, such need although it is early to evaluate its performance and it is still a work in progress.

[6] Available at: https://www.esmo.org/guidelines/esmo-mcbs

Assessment of volume

With respect to the expected volumes of patients per indication, the recommendation would be to correctly use the registries with clinical data, and improve on the basis of learning by doing. Under the experience of payers, many times the expected demand from patients for different indications has been erroneous, much lower than the actual demand. As a result, the budget spent on the purchase of certain medicines was much higher in reality than expected. An effort should be made to reduce these errors in the expected demand so that the weighted average (in terms of volumes) would be much more in line with reality and also to improve the decision on price taking into account the budget impact analysis. Related to that, the Directorate General of Pharmacy in Spain has acknowledged the use in the last three years of a pharmaceutical spending ceiling formula for 14 innovative medicines for which the volume of patients in which they were to be used was uncertain.

Revision of the single price

A revision of the single price for the product should take place every time a new indication is approved for financing. The revision should take into account not only the expectations of volume and value from the new indication, but also a revision of the previously approved indications.

With respect to the new indication, the economic evaluation exercise should follow the guidelines in terms of format and content previously approved by the Ministry of Health.

The review of previously approved indications should be simple in relation to sales volume, and include a report in which it is compared current volume of sales with what was projected in previous reviews. If there had been significant deviations in previous assessments, they should be taken into account in current projections and in the negotiation of the new single weighted average price. In relation to the added value of previous indications, updated information on the clinical benefits derived from the treatment should be incorporated, especially in the case of indications in which there was an accelerated approval procedure with the aim of reducing the time required for actual patient access to the product. It is important to note that the revision of the single price could be upward or downward depending on new evidence on the added value to be provided.

3.3. Advantages and disadvantages

Advantages of the implementation of the single price

Because in Spain there is only one listed price per product, this alternative might be easier to manage, as it continues with that unique single price. Hence, from the regulatory point of view, this alternative seems feasible.

The existence of only one listed price per product gets rid of the incentives for arbitrage that might exist in the case of multi-indication medicines wihtout indication specific discounts that may take place at the local or regional payer level. The theoretical incentive of arbitrage would exist with different prices for different indications of the same medicine, especially if there is a significant difference in the added value (and listed price) of the different indications. If viable, the buyer might try to buy units of the lower price indication to be transfer for the use of higher price indications. As a consequence, this advantage of eliminating the risk of arbitrage is greater when the differences in added value of the several indications is significant. In any case, the literature has shown how it is possible to reduce the risk of arbitrage through for instance, personalized reimbursement models which would take into account real world data and real world evidence to make reimbursement evolve to the medicine efficacy for different indications throughout the medicine's life cycle (Plaza, 2016).

Disadvantages of the implementation of the single price

Currently there is only one listed price per product. However, the alternative analysed here of a single listed price is completely different. Conceptually, having a single price for all indications of the same product, we are moving away from the concept of value based pricing, that is, in principle, the goal to achieve. However, the implementation of a single price involves as many economic evaluation exercises as indications have been approved for financing. As a consequence, the perceived simplicity of this alternative could be deceptive.

At the same time, the fact that the system should maintain the currently existing flexibility and allow for negotiations for discounts between the payer and companies, detracts from the importance of the list price setting, although the weighted average list price would provide a different starting point for negotiation.

Likewise, once a price is set for a product (for its first approved for financing indication), that first price could condition the price of future indications (with greater or lesser value). This situation may lead to strategies in the application for access to financing by companies. The companies might want to access the market with a high product through a high added value indication and might delay the application for access for other lower added value indications.

For instance, if the listed price for an approved indication is very low (it could happen for different reasons, for instance a low added value or a market structure in that indication with high degree of competition and maybe even with presence of biosimilars) it might reduce incentives to apply for access for new indications which would add greater value in order to avoid lowering price. Also, there could be delays in the commercialization of indications that have already been authorized for fear that their commercialization will lead to a reduction in prices for all indications, or because the price set will not be sufficient for a small number of patients. In sum, strategic behaviour could result in the lack of launching approved indications because of strategic and commercial reasons, and in the long run, it could even reduce incentives for innovation. These problems will be aggravated by the system of external reference prices applied in many countries, whereby prices charged in one European country may have repercussions on prices charged in other countries.

The risk of strategic behaviour by the companies in their choice of the order of applications for approval and financing for the different indications is perceived as a very important challenge.

3.4. Regulatory framework

Current regulation is insufficient to regulate all the situations that arise, and besides, it is relatively vague, with the consequence that a single price would be feasible without the need for changes. However, as mentioned above, in order to properly implement a weighted average listed price in which both value and volume are taken into account, it would be convenient to define the content and format, with the needed flexibility taking into account the normal differences among the studies, of economic evaluation

exercises, as well as the formula for the weighted average taking into account information from all the approved indications.

At the same time, it would be convenient to change regulation regarding the revision of prices when new indications are approved, or *ex officio*, every for instance, two years, with information not only from the new indications but also from the previous ones (both in volumes and value, as mentioned above). In the particular case of not having new indications in the set period to reach *ex officio* revision of prices, this alternative may seem similar in practical terms to a Multi Year Multi Indication agreement. However, it is not clear that a Multi Year Multi Indication agreement would get rid of the risk of strategic behaviour in the company.

3.5. Practical feasibility and main challenges

This report aims to present the alternatives from a practical point of view, in terms of their practical implementation in Spain, and not simply from a theoretical perspective. As mentioned, having a unique listed price per product is what happens currently in Spain. However, the current system is not ready to revise prices when each indication of the multi indication product is approved for financing, following a new economic evaluation. As a consequence, in the short run, it would only be feasible to implement a mild version of the weighted average, based on volume. That mild version of this alternative is far from the goal of using full economic evaluation analysis into the equation of the single price for the multi indication product. In fact, price volume agreements have been implemented in Spain for a long time and they are criticized for not adding added value into the equation.

With respect to the challenges, in order to implement (in the medium and long run) an appropriate version of the weighted average price, it would be necessary to generalize and standardize the use of economic evaluation for every indication, as mentioned above.

Also, the performance of the increasing number of economic evaluations would need a very complete Clinical Data Registry that should be as homogeneous as possible among the different Autonomous Communities. That registry should allow for indication specific tracking, although it would be costly to implement and it is not yet clear how or by whom this cost should be borne.

It is important to take into account that the authorization and approval for financing of new indications for an active principle with a high price may result in a budgetary impact problem. In order to reduce the problems derived by that, it should be possible to control and monitor compliance with the objective set in relation to the budget impact analysis previously presented by the company. In the payers' experience, it has happened that the budget allocated for a product was significantly exceeded in reality, leading to a much higher expense for the payer. This threat is greater in the case of a multi-indication product with a single price for all indications, as the expected demand for all indications is taken into account in the calculation of this single price.

Finally, and as mentioned as a disadvantage for this alternative, the existence of a single list price for a multi-indication product may result in strategic behaviour in the company in the choice of indications for which they would apply for approval and financing in Spain. The strategic behaviour is seen by different members of the Expert Panel as a major threat that may delay access for patients suffering several indications because the expected impact of the entry in the market of those indications in the listed price, given the volume of affected patients. A partial solution to avoid this strategic behaviour and the delay in access to patients of some specific indications would be to propose the existence of a single price but with the exception of some indications justified for a very different added value with respect to other indications.

4. Second Alternative: Indication based pricing

4.1. Background

The health economics literature has also reviewed the option of an indication-based price for multi-indication products, in the same cited papers previously (for instance in Persson and Norlin, 2018; Mestre-Ferrándiz et al., 2018; Campillo-Artero et al., 2020; Lawlor et al., 2021) or in Preckler and Espín (2022). In this report, we use the term indication based pricing although in the literature it can also be found as "indication-specific pricing", "indication value-based pricing", "multi-indication pricing", and "multi-indication and combination pricing" as noted in Campillo-Artero et al. (2020). This alternative is equivalent to a unique listed price for the multi-indication medicine but with published and explicit indication specific discounts in what could be named indication-specific discounts.

The main feature of indication based pricing is that it allows for linking the listed price of each indication to its therapeutic value. The rationale for indication based pricing is the search for a model of value-based pricing. Because the therapeutic value of the multi-indication product may differ per indication, an indication specific price would overcome that problem. Thus, through indication based pricing, prices may better reflect the social or individual willingness to pay per indication and improve social welfare with a greater access to the medicine from patients suffering the approved indications (Cole et al., 2018; Campillo-Artero et al., 2020). Also, in the long run, Cole et al. (2018) suggests that indication based pricing provides the right incentives for innovation from the point of the society, and at the same time, it provides more incentives for the entry of products in the different relevant market (indications) promoting a greater degree of competition.

International experiences

The country which present a situation closest to indication based pricing is Italy. Regulation in Italy requires the existence of a monitoring registry with information per indication filled by hospitals and prescribers. That registry allows for Managed Entry Agreements (MEAs) per indication that may take the form of risk-sharing agreements, pay-for-performance, or even a fee for efficacy (Lawlor et al., 2021; Campillo-Artero et al., 2020). The Italian system is managed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), and it allows for a different price per indication in multi indication medicines. With respect to reimbursement, it depends on the net price for each indication and the volume of the product sold for patients in that indication. Depending on the negotiated conditions in the MEA, the company may need to pay back depending on the performance of the product (AIFA, 2015), and most of the financial details of the agreements are confidential (Pauwels et al. 2017). That lack of information is common in many other countries, such as the UK, or even in Spain with respect to the risk sharing agreements. Clopés-Estela et al. (2021), Reyes-Travé et al. (2021) and Guarga et al. (2021) state how The Catalan Health Service (CatSalut) in Spain has established a systematic, traceable and transparent methodology for the design and implementation of risk-sharing arrangements and as of December 2019 had successfully implemented 15 such schemes, although their lack of transparency limits the potential benefit derived from them.

The Spanish context

In Spain, there is no system such as indication based pricing for multi indication products. Instead, there is a unique listed price per product. That listed price represent the maximum price that can be paid for the product and is set at the national level. However, it is important to note that (as previously mentioned also for the single listed price alternative), the system presents flexibility so that payers at the regional and local levels may negotiate discounts with the company below national listed prices. The final price paid by the payer remains confidential. Although in Spain there is no indication based pricing officially, it is likely that currently, some hospitals may be asking for indication specific discounts when buying the product. However, whether there is some kind of indication specific discounts remains unknown.

4.2. Mechanic of indication based pricing

Because currently there is only one listed price per product, if Spain changed to an indication based pricing, it would be necessary to change the regulation in order to allow different prices for different indications of the product. Currently, Spanish regulation specifies “the price of a medicine” in different articles of for instance, the Royal Legislative Decree 1/2015, of July 24, 2015, approving the revised text of the Law on guarantees and rational use of medicines and health products.

If the Interministerial Drug Pricing Commission (CIMP), in charge of setting the listed price of medicines, decided to promote an indication based pricing, or within the single listed price, it would provide indication specific discounts, the Expert Panel would recommend to base the listed price per indication or the specific discount per indication on the added therapeutic value of each approved indication for which funding is authorized, and the expected volume of patients (budget impact analysis), as well as the degree of competition per indication.

In any case, the Expert Panel considers that even with indication based pricing, the current flexibility under which negotiations between providers and payers at the regional or local levels are allowed should still be in use. In other words, even if there was a listed price per indication (maximum price that could be possibly paid), the actual cost of the product per indication could be lower, and most likely confidential, because of private negotiations.

The economic evaluation exercise per indication

Indication based pricing relies on the implementation of economic evaluation exercises per each indication of the product. Because under this alternative, there cannot be access to patients without a price, and that price depends on the economic evaluation exercise, it is crucial to be agile in the execution of that economic evaluation study. That increasing amount of economic evaluation exercises should follow the guidelines imposed and approved by the Ministry of Health, included or not in the therapeutic positioning reports.

Nothing changes, relative to what has been mentioned above (see section 3.2 above) for the first alternative, with respect to how the economic evaluation exercise should be performed regarding the assessment of clinical benefits and value, measure in quality of life, the concerns regarding the use of willingness to pay, or the assessment of volume per indication, that should use if possible a complete registry of clinical data and be revised every time that it is needed to perform a new economic evaluation exercise for the same product because of approval of new indications, in order to improve the quality of the budget impact analysis.

Revision of the indication-specific prices

Once a product obtains a specific listed price for an indication, there should be a periodic revision taking into account the updated information available both in terms of value and volumes since the last revision. With respect to volumes, there should be a revision regarding how well the expected volumes per indication matched real sales for patients of that indication. The results of that revision should be taken into account provided the influence of the budget impact analysis in the listed price for that specific indication. With respect to clinical benefits and value, the registry of clinical data should help to find out whether there should be an update of the value assigned in the previous evaluation. That is especially important in the case of products with conditional marketing authorization by the EMA whose approval has been accelerated at the European level. Also, the evolution in the market structure of the indication should be taken into account, which means, to look at which other products are present as alternatives within that indication, how similar their clinical benefits and prices are, and the degree of competition.

4.3. Advantages and disadvantages

Advantages of the implementation of indication based pricing

The main advantage of indication based pricing or indication based discounts over a listed price is that it follows the recommendation of value based pricing, in the sense that each indication of a medicine is treated as a different product. Following that strategy economic theory explains how social welfare is improved, through improved access, and in the long run, companies receive the right incentives for innovation, and the degree of competition at the different indications increases. In fact, an extreme case of indication based pricing that has already been used, would be to commercialize as different products, the same product for different indications. Actually, with indication based pricing or indication specific discounts, the threat of the strategy in companies of commercializing one or other indication before to protect prices would, in principle, be solved, precisely because the different indications do not share the price and the companies do not fear that the price of one indication will drag down the price of the others, as in the alternative where there is a single listed price.

Also, another advantage of indication based pricing is that it allows for taking into account in the listed price that even if the product is the same, the development stage per indication may have been different, with different R&D expenses which mostly depend on the clinical trial.

In Spain, the current system offers flexibility that allows for negotiating prices between payers and companies through confidential discounts. In this alternative, those confidential discounts would be indication specific. That flexibility could facilitate indication based pricing.

Disadvantages of the implementation of indication based pricing

Indication based pricing needs economic evaluation exercises for all indications of a medicine, and the need to repeat the price setting per indication. The need of evaluation is not a disadvantage of IBP per se, as evaluations (with or without economic content) are already performed through the therapeutic positioning reports, and the performance of economic evaluation is also needed for a weighted-average price. However, the number of needed economic evaluations would be multiplied with respect to current numbers and thus, resources and time should be allocated to that task. It is still to be evaluated whether the structure that is being developed in Spain for those economic

evaluations is going to be sufficient and whether the speed at which these reports should be issued will be adequate to avoid delays in patient access to the medicine for each new indication.

With indication based pricing, the number of listed prices would be multiplied and the number of purchases per provider of the product could also be increased. The management of that situation with the bureaucracy needed within the regulation regarding public purchase in Spain might be more complicated than a single price.

With different prices per indication, buyers might have incentives for arbitrage. In order to counteract those perverse incentives, the registry of clinical data has to be very closely monitored, to check that the uses of the product correspond to the indications that have been reported in the purchase. In any case, the risk of incentives for arbitrage is greater or lower depending on how different are the indications and the administration of the product to patients of the different indications. In that sense, when administration to patients is very similar or even simultaneous for different indications, the management of the product for those indications would be extremely complicated with respect to the purchase, invoice, and monitoring of the administration. The same problem would arise with medicines used in agnostic tumours, which are equally applied to different indications. These cases could be treated as exceptions and be left out of the practice of the indication based pricing.

Although we have mentioned that IBP might be benefited by the flexibility in the Spanish model that allows confidential discounts that might be indication specific, such flexibility could create the perception in many payers that it is not necessary to have different prices for indications because they are already negotiating it as they see fit. In any case, indication-based pricing would allow all payers in Spain to start product negotiations for each indication from the same starting point, with clear information on the added value of the product per indication.

4.4. Regulatory framework

In order to be operational the indication based pricing strategy, first it would be necessary to reform the regulation to allow for different prices for the same product, as current regulation always refers to the listed price as a price per medicine. A way to avoid this need would be to consider and commercialize the same product at different markets as

different products, with different trade name. That has been done previously and could be done again. However, that would multiply the number of products in the market. Also, it is noted that in many occasions, a product is administered simultaneously through vials for patients suffering different indications, which would prevent it from being marketed separately. As a consequence, the option of separate commercialization of products per indications would not be always feasible and could be analysed for other scenarios, with independent administration to patients or with significant differences among indications that ease the monitoring of the use of the medicine. A different way to avoid the need of this reform would be the adoption of a unique listed price for the medicine, together with indication specific discounts following the information in the economic evaluation and budget impact analysis.

As in the case of the previous alternative, it is needed to regulate the content and format of the economic evaluation exercises per indication, and with respect to the assessment of value and volumes, so that the time needed to perform the evaluation is shorten as the delays in the access for patients to the medicine.

Regulation should maintain the current flexibility in negotiations between payers and companies to pay prices below listed prices. With that flexibility, some payers at the regional or local level might present some resistance to this change or simply not see the sense in it.

Also as in the case of the previous alternative, it would be convenient to change regulation regarding the revision of prices, *ex officio*, to be performed periodically, for instance, every two years, with the new information collected about the product in each indication (in value and volumes), and the evolution of the market structure for the indication.

4.5. Practical feasibility and main challenges

In order to be feasible indication based pricing or indication specific discounts over a listed price in Spain, first, it would be needed to provide the necessary regulatory changes regarding setting (listed) prices by relevant market or indication instead of by product. That change should not be complicated to undertake even if it takes some time. The alternative of considering the commercialization of the multi-indication product as different products in different indications would also be feasible and more direct (and

recommended for some members of the Expert Panel), except for some situations, as the case of simultaneous administration of the product to patients of different indications, that would make impossible to separate its purchase and consumption and monitoring, or the case of medicines used in agnostic tumours. Another alternative to the regulatory change is the use of indication specific discounts with a unique listed price for the multi-indication medicine.

As in the case of the alternative of the single price, a major challenge for the feasibility of this alternative is the need to perform an increasing amount of economic evaluations (generalized and standardized use) and, for the new indications, and the periodic revisions. Only once a structure able to perform those economic evaluations be set, indication based pricing would be feasible. Obviously, a necessary condition for that is the development of a Clinical Data Registry that allowed for the monitoring of the use of indication specific information in the economic evaluation studies. That Registry should provide as homogeneous as possible information in the different regions. Its implementation would be costly, at least at an earlier stage. That registry should be used also in the budget impact analysis for setting the price of new indications and in the revision of other indications approved for financing earlier, in order to correct any deviation with respect to earlier estimations.

A feasible possibility in the medium run would be to use the economic evaluation of the product for each specific indication when approved to provide those indication specific discounts for a single listed price of the product, resulting in maximum prices per indication, that afterwards can be renegotiated by the payers at the local and regional levels.

It has been mentioned as a disadvantage that there might be some resistance to this alternative if it complicates the bureaucracy of purchase, invoicing and monitoring the use of the medicine. It is important to note that it is very likely that currently there are hospitals obtaining indication specific discounts through confidential agreements, and implementing indication based pricing (different listed prices per indication or indication specific discounts to be applied to the single listed price) would affect the way in which providers at the local and or regional levels privately negotiate prices with the companies through confidential agreements. The objective (and challenge) here would be to provide, at the macro level, transparent maximum listed prices per indication.

Hence, in the medium and long run, this alternative would be feasible if the governance and regulatory framework evolve and are reformed in the mentioned directions.

5. Discussion

The increasingly common presence in the market of multi-indication oncology treatments, with different clinical benefits per indication, is an important challenge in terms of pricing and reimbursement for health systems, since a unique price is incapable of reflecting the real value of the medicine. In this report we present two of the methodologies that are discussed to help in the management of that challenge: a single listed price per product, or indication based pricing. Each alternative has its own pros and cons. Other methodologies such as the use of MCDA or Specific funds could be combined with the alternatives discussed here but are not the focus of this report.

The alternative of a unique single price for all the indications of a product is in principle easier to manage, and in terms of regulation, it would not need major modifications to be operative, as a single price per medicine is what we have currently in Spain. At the same time, a single listed price minimises the risk of arbitrage, which could lead the provider to purchase the product at the price of a low price indication for use in patients with another, more expensive indication, where monitoring of the use is complicated. However, having a single price moves away from the value-based pricing. Also, in order to properly implement this single price per product, economic evaluations need to be carried out systematically, rapidly and homogeneously for all new indications and periodically for all indications already authorised and approved for financing. The goal under this alternative is to avoid the use of a simple price-volume agreement for the medicine (this method could be complementary as a consequence of the budget impact analysis) and set a single listed price that is calculated as a weighted average taking into account the added therapeutic value of each approved indication for which funding is authorized, as well as the expected number of patients that could be benefitted, also from each indication. This single listed price would become the maximum price for the medicine at the national level, and local and regional payers might negotiate lower prices (maybe per indication) with companies, although with a different starting point at the negotiations. The price should be revised every time that there is a new indication approved and periodically to check new clinical evidence on the indications as well as possible deviations in the estimation of the demand. Maybe the greatest concern of a single price is that if not implemented properly, the ultimate goals of accelerating access

to innovative medicines for patients together with the sustainability of the health system and providing the right incentives for research and development could be missed, either because of the inability to carry out the economic evaluations quickly and thoroughly, or because of the business strategy of deciding not to apply for market access for certain indications because the variation in price for all indications of the product is not compensated. Payers perceive the risk of strategic behaviour by companies in the entry of products as very high. In addition, the international reference pricing mechanisms existing in many European countries could pose another difficulty for the correct application of this alternative.

The alternative of indication based pricing (IBP) is closer to the goal of promoting value-based pricing, as it provides a different price, based on the value evidenced in the economic evaluation exercise to each approved indication, and in the long run, it improves social welfare and provides the right incentives for innovation and a higher degree of competition in markets. International experiences in IBP are based mostly on confidential Managed Entry Agreements and risk sharing agreements, which limit the degree of transparency in the markets. It would be challenging to implement IBP in Spain. First, because regulation should, in principle, evolve to allow for different listed prices for the same product, or at least, allow for indication specific discounts and periodic revisions with updated clinical information as well as any deviation in the expected demand. Price-setting should also take into account budget impact analysis and the market structure per indication. Second, because it, again, makes necessary to carry out systematically, rapidly and homogeneously economic evaluation exercises for all new indications and periodically, their revisions. Thirdly, because there could be resistance from local and regional providers and payers who are already negotiating (and should continue to do so) discounts that could be indication-specific, as they might feel that their bargaining power is lower with IBP, while it just would modify the initial point of negotiations. Also, strict regulation regarding public procurement might be more tedious with different prices per indication, or in the extreme version of IBP in which different indications are commercialized as different products, preferred by some experts when feasible; and the risk of arbitrage would exist if monitoring were not performed carefully.

Both alternatives, a single price and IBP, might admit exceptions. IBP is not always feasible. For instance, it is unfeasible in the case of agnostic tumours or when the administration of the medicine is not independent by indications. Those cases should be treated as exceptions in the case of implementing IBP. At the same time, if there are specific indications with enormous differences in added value with respect to the other

indications, a single price strategy might admit exceptions. For instance, to avoid the risk of the company deciding not to market a low added value indication, which could reduce the price of all other indications, it could be a differential price for that low price indication, and a single price for all other indications.

Hence, both alternatives present pros and cons for their implementation. However, it is important to note that both of them share some common challenges.

- The appropriate implementation of both alternatives relies on the existence of regulation promoting systematic, rapid and homogeneous economic evaluations for all innovative products and all the new indications of them and periodic revisions, and in the existence of a structure capable of performing in a timely manner all those economic evaluations in order to reduce the time for the patients to access the medicines (once the submission is done by the companies). This is a challenge in Spain because even if economic evaluation is mentioned in the regulation and mandatory, at least the perception by different agents is that its use is not as systematic as it should. Last year, the Network for the Evaluation of Medicines in the NHS (REvalMed) was launched with the aim of implementing economic evaluation in the therapeutic positioning reports (IPTs) of innovative medicines or in their new indications. The first report following this format, including economic evaluation, was published in June 2021. Whether REvalMed will be capable of performing all needed economic evaluation exercises and with the intended transparency in their required content to avoid uncertainty in the market, or whether economic evaluation should be included in the therapeutic positioning reports is still to be seen. However, given the increase in the presence in markets of multi-indication products, and its expected evolution, the structure of such Network should be large because the number of assessments increases the administrative burden and may delay access. It is a huge challenge to implement such system, taking into account that in Spain, economic evaluation has not yet been implemented in a precise, sophisticated and transparent manner (for only one listed price per product). Many Spanish health economists have implied the need of an independent Agency, inspired in the NICE, to help in this matter, and for instance define the threshold that should reflect the maximum social willingness to pay for one QALY.

- The systematic performance of economic evaluation per indications need very complete and robust data systems, which at least in an initial period might result

in huge implementation costs. It remains to be discussed whether this cost should be borne by the regulator, the companies or shared by them. The Registry of Clinical Data should include specific and as complete as possible information regarding the indication for which the product is purchased, and monitor its use for patients per indication, the added value and health outcomes obtained, or adverse effects. In this way it would be possible to avoid incentives to arbitrage, and at the same time, to make accurate estimates of the expected volume of patients who might demand the product for each indication, or to correct past estimates by calculating the deviations that could be used in price revisions, and to update information regarding the clinical benefit of the product better than trusting in the estimations provided by the companies. This Registry should be as homogeneous as possible for all Autonomous Communities. This represents another challenge because not all Autonomous Communities are in the same place regarding the registry of clinical data and the listed price setting and the periodic revision of all listed prices should be performed at the national level. It is necessary to evaluate the cost of implementing such structure, since as mentioned in the literature, the increase in administrative costs associated with the identification of indications, the differentiation of value and the purchasing and payment process may be higher than the benefits derived from the new pricing system (Campillo-Artero et al., 2020). In fact, it is noted by the Expert Panel that all this effort of developing the Registry of Clinical Data and the structure for performing economic evaluation should not be made just to determine the price (single price for the product or per indication), especially since at local and regional level, discounts for indications already exist, even if they are confidential. It is more important to focus this effort in the clinical benefit obtained by the patients, through earlier access or better information on the clinical outcomes of the medicines. Although Spain has significantly improved its information systems in recent years, they are still far from achieving the necessary accuracy. In this regard, it is important to bear in mind that one of the objectives of the Recovery, Transformation and Resilience Plan for which there are European funds is precisely to work on the digital health plan and this Register could be included in it.

- There might be reluctance to change in providers and payers at the regional and hospital level, as they are used to negotiate discounts directly with companies, and most likely, taking into account the volume of patients per indication. They might believe that they have less bargaining power, but what would change would

be the list price, which is the starting price, either of the product or of each of its indications approved for funding. The flexibility in negotiating discounts at the local or regional level, no matter the chosen alternative, is seen as necessary, although confidential agreements such as Managed Entry Agreements in place limit the principle of transparency of information and thus, the promotion of a greater degree of competition.

Hence, both alternatives could potentially be used in Spain in order to accelerate the access to medicines for patients, each of them with their advantages and disadvantages, once the registry of clinical data is in use and the structural problems that prevent the systematic use of economic evaluation are solved. At the same time, those alternatives could be used together with other complementary methodologies such as budget impact analysis (and its revision, at the same time than the revision of prices), the analysis of the degree of competition at the different indications, or even multi criteria decision analysis or cancer specific funds that have hardly been presented in this report.

6. Conclusion

This report presents the feasibility of two alternatives that potentially could reduce the delay in the access to approved multi-indication oncology products at the same time than fostering innovation and the sustainability of the Spanish Health System, under the perspective of a multidisciplinary Expert Panel: a single listed price for all indications of the product, and an indication based price system. By explicit request of the Members in the Expert Panel, this report does not provide any specific endorsement for one or another. Differently, it presents their advantages and disadvantages given the context in Spain in order to inform the decision makers and help them in their decision of a methodology. None of them is perfect. Indication based pricing is more aligned with the goal of value based pricing, although its implementation may present difficulties and an increase in administrative costs in the purchasing and payment processes, and it may result in arbitrage. Differently, a single listed price, even if calculated using a weighted average approach based on added value and expected volumes may result in strategic behaviour by the companies.

In order to attain an appropriate implementation of any of the two alternatives, Spain should provide a regulatory and structural framework in which a registry of clinical data be operative and help the performance of systematic, rapid and homogeneous economic

evaluation exercises for all new indications in order to help in their price setting, and periodically, in their revisions.

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