PAY PER RESULTS SCHEMES IN ONCOLOGY

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As well as exploring the extent and focus of innovation in oncology, the following is an analysis of the accumulated experience in shared risk agreements, one of the measures aimed at achieving the difficult balance between pricing new treatments in consistency with their efficiency and safety, to provide the industry with reasonable benefit in order to sustain investment in R&D and to guarantee*, at the same time, the access and the sustainability of the health system.*

What is the extent and focus of innovation in oncology?

The incorporation of therapeutic innovations must ensure the balanced achievement of a triple objective: the guarantee of granting patients with access to solutions that are truly effective, the efficiency and sustainability of the system and the compensation of the innovative effort. But first we must define what *innovation* is exactly; no definition of the term has become the definition of international reference. They are incomplete and vague, although some of them are extremely clear (the first motorcar, plane, submarine or physiological serum; the first light bulb; penicillin; *reading* DNA), and others are of a much smaller magnitude, incremental, gradual (the umpteenth ACEi, model of a car brand or pacemaker). Classified in this way, they offer a blunt approach to the degree of innovation, but are nevertheless intuitive (Puig-Junoy and Campillo-Artero, 2019).

The International Society of Drug Bulletins has proposed three types of innovation in terms of medicines (Kopp, 2002): commercial, technological and advances in therapy, that is, those that benefit patients when compared with the standard treatment. Obviously, this last type of innovation is of great interest to us. And, to decide what to include in the portfolio of services from the perspective of efficiency and social welfare, it is imperative that we differentiate innovation that is disruptive from that which may be considered marginal.

How do you innovate with medicines and, specifically, oncology?

There is the technological innovation of new treatments. We have gone from having medicines which are very small molecules, simple in structure and with just one usage, to having biological medicines, obtained from living beings, with enor-

mous relative molecular masses and remarkable structural and functional complexities (erythropoietin, monoclonal antibody fragments, complete monoclonal antibodies, molecules bound to antibodies, etc.). Today, we administer viruses (innocuous and carrying genetic information that integrates into the human genome), oncoviruses (which attack tumour cells), and whole cells, such as genetically modified T lymphocytes.

There is innovation in pharmacodynamics (what medicines do to the body): there are medicines that inhibit the action of enzymes (tyrosine kinase, for example) which affect the regulation of the life cycle of cells, including tumours, and monoclonal antibodies that block the receptors in these cells preventing them from being attacked by lymphocytes (*check point* inhibitors); molecules that prevent the growth of tumour vascularisation or specifically damage the DNA of cancerous cells rendering their natural cycle deficient when they come to be repaired (poly-(adenosine-pyrophosphate-ribose) polymerase), and medicines that perform several of these actions simultaneously.

There is also innovation in other areas, such as the development of new biomarkers in oncology and other specialities (although their diagnostic validity, clinical utility and discriminatory capacity vary considerably and they have not all been adequately validated) and with artificial intelligence models that improve the diagnostic, prognostic and predictive capacity of response and toxicity, combining information from different sources.

What is the extent of the innovation?

Besides the innovation described, if we focus on the definition of innovation as a breakthrough in therapy, evaluations carried out in recent years clearly show that the benefits of marketed treatments vary depending on the drug analysed — paradoxically, lower than expected in the design of the clinical trial — and the price of which, as a common denominator, bears no relation with the benefit provided.

A recent analysis (Wieseler, 2019) by the German Institute for Quality and Efficiency in Health Care (IQWiG) on the contribution of 216 oncological and non-oncological pharmaceuticals authorised between 2011 and 2017 indicates that 25% provide a benefit that is considered greater or considerable; 16%, less or unable to quantify, and 58% offer no benefit in terms of mortality, morbidity or quality of life.

Another specific analysis of the 51 oncological pharmaceuticals approved by the FDA between 2000 and 2015 shows that, according to the clinical benefit scale of the European Society of Medical Oncology (ESMO-MCBS), only 35% have a significant clinical benefit (level 4 or 5) and, according to the American Society of Clinical Oncology (ASCO-VF), the range is from 3.4 to 67, with an average of 37. Equally, it highlights that no relation has been found between the contribution of clinical benefit and the commercial price (Vivot, 2017).

In conclusion, there are some very promising advances in pharmacodynamics and technology with incremental therapeutic value which, at the moment, is mainly low, and a price that has little relation with the benefit provided (Workman, 2017).

The challenges of innovation in medicine from the viewpoint of R&D and the regulator

Motives aside, the productivity of R&D (new medicines authorised by resources invested in R&D) has reduced gradually over the last few decades (productivity paradoxes). Incremental *improvements* in health are lower than expected whereas the costs are rising. The failure rate of the development of new medicines (from phase I to when they are authorised in oncology varies globally between 70% and 90%) highlights their complexity (difficulty in proving proof of concept in phases I and II; insufficient pharmacodynamic and pharmacokinetic results; progression to phase III with insufficient results from phase II; difficulty in extrapolating mechanisms of action and targets from one disease to others; errors in the evidence, in pivotal superiority trials, of efficacy and safety versus placebo in a new treatment or active control, or only marginal benefit or therapeutic equivalence). Also, the extension of the R&D period reduces that of cost recovery during the monopoly granted by patents (Dowden and Munro, 2019; Heemwong and Siah, 2019).

The industry's main challenge is to recover its investment in R&D (including capital costs and those of failures) and make a profit. That of the regulators is to ensure that the new therapies comply with the regulatory standards of effectiveness, safety and quality, and that their prices make them accessible to patients without undermining the efficiency and sustainability of the system and for the manufacturers to recover the high costs of R&D (fixed and sunk), authorisation and production plus a *reasonable profit margin* (Campillo-Artero, 2016).

Achieving all of this means overcoming many barriers. In the clinical trials, even those that are well designed and carried out right through to phase III, with a substantial sample size and a long duration, as in all studies, all estimates of the causal effects of treatments (efficacy and safety) have an associated element of uncertainty; it is consubstantial to them. Over the last few years, early authorisations (even in phase II) of promising treatments seek to promote early access for patients who may benefit from them. This increases the aforementioned uncertainty (*evidence*) and the result is summarised by the *evidence versus access* aporia.

If we add to this the asymmetry of information between producers, regulators, prescribers and patients; a regulatory system that is no longer binary (either it's authorised or it's not authorised), and regulatory errors: authorising a treatment very early on which turns out to be neither effective nor safe in the end or, although it is efficient to a certain extent, its risk/benefit balance is inadequate (type I), delaying its authorisation when it is subsequently proven to be efficient and safe, thus depriving patients of its benefit or delaying it (type II), and the opportunity costs associated with both errors (type III) (Eichler et al., 2008).

As well as relatively low *efficiency and* safety, the prices and spending on new oncological medicines continue to increase greatly and are a threat to the efficiency and sustainability of the system. Numerous investigations have proven this: their price is not the *socially* optimal price (the lowest so that the producers recover the R&D and production costs; a little higher than the marginal cost so that the innovator makes a *reasonable* profit) and lower than the maximum that society is willing to pay. However, current prices are so high compared to the marginal cost that the producers not only recover the R&D and production costs (including those of capital, failures and the authorisation process), but they also aim for very substantial investment returns. The consequences of reductions in productivity are offset by a sharp increase in prices, which does not justify the low relative efficiencies observed. This unbalances the distribution of the social surplus: the producer's profit (greater) plus that of the consumers (smaller).

How are these challenges being faced?

To reduce limitations, inefficiencies and negative externalities and proceed with facing the challenges highlighted in the industry, over the last decade and a half, the regulators and citizenry have been introducing reforms in *assessment*, coverage, funding and reimbursement *appraisal*. Due to a lack of space, these are summarised in table 1, although some of them still need to be postulated.

Table 1. Improvement measures for regulating medicines

In authorisation
• Promotion of the use of new experimental designs: *basket*, *umbrella*, platforms and those that remove the barriers between phases I, II and III (*seamless drug development*).
• Improvement of information on *safety* in clinical trials (PK/PD studies, risk-benefit assessment, risk tolerance thresholds, validation and qualification of biomarkers, prediction of toxicological profiles using *in silico* models, reinforcement of pharmacoepidemiology and results reported by patients.
• Incorporation of technical validity, clinical validity and utility as standards for regulating diagnostic tests, including biomarkers of diagnosis, prognosis, response and toxicity associated with drugs (*co-development*), to improve their validity and diagnostic performance.
• Review of uncertainty thresholds to reduce regulatory errors associated with authorisations and their consequences.
In coverage, pricing and post-authorisation
• New schemes for authorisation and access to new medicines: *priority review*, *fast track designation*, *early access*, *accelerated approval* and *parallel review*.
• Authorisations based on relative effectiveness and safety as opposed to absolute, and reinforcement of the monitoring of their fulfilment and of the regulatory and conditional standards (*law enforcement*), such as that limited to a subgroup of patients and subsequently expanded with new evidence, *adaptive pathways*.
• Greater and better use of economic evaluation as a fourth barrier.
• New pricing models, such as *value-based pricing*.
• New coverage, funding and reimbursement schemes (*coverage with evidence development, patient access schemes*), and shared risk agreements.
• Reduction in disparities and between criteria for authorisation, coverage, pricing and reimbursement between regulators, funders and health technology assessment agencies.
• Reinforcement of post-marketing surveillance and *comparative effectiveness*, *big data*, *real world data* and *machine learning* to increase and improve the information and prediction of effectiveness and safety post-authorisation.

Insufficient compliance with authorisation standards, coupled with the increase in early authorisations (conditional or not) requires, on the one hand, an increase in post-authorisation monitoring to gather information on effectiveness and safety, reduce uncertainty, and control the effects of increased usages, of *reversals* and inadequate substitution (including compassionate and unauthorised use). On the other hand, the use of dynamic coverage, pricing and financing models, adapted to the progressive results of the aforementioned monitoring.

Despite the already fairly widespread tendency to recommend value-based pricing systems, there are controversies that reveal that we should not lose sight of the economic theory on which they must be based (depending on their true characteristics, their effects may differ from those expected), that not all practical applications correspond to these models themselves and, in the absence of *pure* models in practice, shared risk agreements could be considered the closest approach to these models (Campillo-Artero, et al., 2019). The additional resources that all of this implies (the transaction costs are high) must be anticipated along with an assessment of the extent to which the marginal social benefits of the reforms are greater than their marginal social costs.

The evaluations of these reform measures (table 1) indicate that their implementation varies considerably between countries and that, all in all, they are solutions that are partial, slow, provisional, insufficient and must be adapted to changing conditions in the short, medium and long term, without forgetting that some are structural. The loss of social welfare (that of everybody) due to negligence or regulatory inefficiency can be extensive.

The Gordian social knot consists of an intricate balance: compliance with minimum regulatory standards of efficiency and safety, adequate thresholds for aversion to uncertainty and error tolerance, notable health benefits, and prices and measures (like the monopoly of patients), so that the industry recovers its expenses and keeps investing in R&D without diminishing efficiency, sustainability and the solvency of the system. Below, we will examine whether shared risk agreements (just one of these measures) may contribute to the *untying* of said knot.

Pay per results schemes (PRS) as an alternative to the traditional scheme

Faced with this scenario of uncertainty in the evaluation of innovation, which goes hand in hand with a highly standardised medicine pricing system, which is failing to respond to the uncertainties raised (Espín, 2010), new models need to be developed and validated. In Spain, decisions regarding the incorporation of therapeutic innovations into the Basic Services Portfolio of the National Health System (NHS) and setting their prices, access conditions and funding are one of the State's direct responsibilities (Law 29/2006, of the 25th of July). However, the decentralised territorial areas of the NHS are responsible for their own management and funding, along

> *"In Spain, the incorporation of therapeutic innovations into the Basic Services Portfolio of the NHS and setting their prices and access conditions are one of the State's direct responsibilities"*

with the development of measures to guarantee equitable and efficient access (Segú, 2014). In turn, public hospitals have to adjust the procurement of medicines to systems that, due to their rigidity, do not allow for major changes and in these systems there must be, and there are, opportunities. Below, we will analyse how PRSs may not only be an option based on value payment models, but also on information feedback models with *real-world data*.

Medicine payment schemes have traditionally focussed on the inclusion or exclusion of a certain medicine in the portfolio and on negotiating a price, in theory, according to its contribution in terms of benefit and the volume of the population that is likely to be treated. In these schemes, the price is fixed, regardless of the results and adequacy. In the event of new usage of a medicine which has already been marketed, the price usually changes, but it is still fixed, regardless of the differential contribution between the usages. The fundamental characteristic of these schemes is that the buyer assumes all of the risk, both budgetary and regarding the impact in terms of health deriving from usage and the results of the medicine in real practice (Segú, 2014).

These traditional systems find it hard to face up to the challenges implied by innovations, especially the uncertainty surrounding comparative effectiveness and safety, budgetary impact and cost-effectiveness. Some countries have added to these traditional systems, including prioritisation methods based on incremental cost-effectiveness thresholds that show the social ability to pay, such as that of NICE England-Wales, which leads to a "yes/no" decision regarding inclusion in the portfolio. Additionally, they have the advantage of being transparent decision-making systems; they have an influence on the portfolio and, laterally and not always, on the price, and they act upon local decisions, although they do run the risk of creating endogenous prices.

> *PRSs are an approximation to value-based payment and have the advantage of providing real-world data that provide feedback for the decision-making system*

In terms of this traditional pricing system, there is currently some discussion among academics and also on social media proposing the use of information on development costs when calculating the price. In this regard, the World Health Assembly recently approved (28th of May, 2019) the ruling *Improvement of the transparency within markets for medicines, vaccines and other health-related technologies*[1], which has a series of guidelines for the States to improve access to information on the different R&D processes and pricing, and improve collaboration between them and the health systems. It is designed to give governments the information that they need to negotiate fair and affordable prices.

In terms of the challenge of new medicines, the uncertainties when evaluating innovation and traditional payment schemes with fixed prices, in some countries flexible access models have been put forward and implemented. The common denominator in all of these models is that the benefits and risks associated with these uncertainties is distributed between the supplier and the healthcare system. For this reason, they are called *shared risk agreements* (SRA), although the naming varies and they are also known as *patient access scheme* (PAS) (Carlson, 2010; Garrison et al., 2013) or *managed entry agreements* (MEA) (Pauwels, 2017). These flexible access models for medicines cover a wide range: from financial models, such as price-volume or spending ceilings, to results-based agreements.

When these results-based models are applied on an individual scale, we are talking about PRS. Here, the health system only finances the cost of patients who respond to treatment within a certain period of time. PRSs are an approximation to value-based payment and, what's more, have the advantage of providing real-world data that provide feedback for the decision-making system. They also aim to include the co-responsibility of the industry in sustaining the health system and evaluating health results, that is, progress in reducing uncertainty with more awareness of the effectiveness, safety and cost-effectiveness of medicines in healthcare practice and, finally, providing therapeutic solutions for patients based on the clinical results obtained. We will spend more time discussing the experience gained with PRSs, since PRSs are the SRAs that provide the most value, because in their application the price of innovation is dynamically linked to their conditions of use and to the results obtained in real practice.

As an article of special interest, it is worth highlighting the one published in 2013 by the *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR) (Garrison et al., 2013) with a stance on good practices for the design, implementation and evaluation of SRAs, including PRSs.

Implementation experience with PRSs

A recent report by the consultancy Ernst & Young (2019) on the application of access models on an international scale highlights the fact that they focus on the five main European countries: Germany, Spain, Italy, France and the United Kingdom. It identifies that oncology is the therapeutic area where they are used the most (38% of the agreements signed).

Financial schemes are the predominant ones (57%) while those based on results make up 23%. In terms of Spain and flexible results-based models, Catalonia and Andalusia are the most active communities reviewing the experience of SRAs with oncology medicines in Europe and finding that it is a common policy used by payers to ensure access to high-cost oncology drugs (Pauwels, 2017).

Ultimately, there are four basic elements that must be assessed in decisions for defining which payment scheme is the appropriate one for a given medicine/prescription (Segú, 2014): aspects related to the medicine and the prescription, the existence of a degree of significant uncertainty, willingness to pay and instrumental and organisational elements of the environment of application. This last element has a particular impact on the appropriate organisational and instrumental conditions in the environment that allow for its operational application.

1 https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_ACONF2Rev1-sp.pdf.

When defining the outcome variable, it is especially important for the objective to be clear, measurable, objective and relevant to the clinic. If surrogate variables are used, they must be good predictors of the end variable (tumour response *versus* overall survival) and the model must always be based on routine clinical practice and not on creating new structures or requirements.

The maximum objective and value provided by incorporating PRSs into the work dynamic of an institution is the focus on aligned results between the professionals, managers of the institution and the pharmaceutical industry. If we break down these objectives and incorporate other benefits provided, we could indicate that PRSs:

- Allow the reduction of uncertainty inherent to incorporating new medicines into the health system, by sharing the associated risks between the health funder and the supplier.
- Favour the medicine being accessible to the target population and avoid the prescription of medicines in unauthorised usages.
- Satisfy clinicians, reducing their uncertainly.
- Limit the budgetary impact if the defined health benefit does not occur.
- Make it possible to export and share the results obtained in a robust manner to the practice of care outside of the clinical trial.
- Offer guidance to the pharmaceutical industry in the search for the best medicines to achieve a balance between quality and economic profit.
- Build bonds of trust between the academic world, that of healthcare and the pharmaceutical industry.

To develop experiences, it is important to be aware of the barriers for the implementation of PRSs, among which the following stand out:

- Their implementation requires powerful information systems that allow the effectiveness of the treatment to be monitored reliably, something that can be complex and costly depending on the illness in question. A report by the *Cancer Network Pharmacist Forum* (2009) alerted to the fact that the SRA schemes that up until then had been implemented in the United Kingdom were too complex and had variables that were not covered in care practices. For this reason, PRSs may have high implementation, follow-up and monitoring costs.
- They imply a significant bureaucratic burden and high administrative and financial costs. Also, the necessary negotiations are lengthy in terms of time.
- They are highly complex, depending on the characteristics of the technology in the agreement, especially when the agreed results are uncertain and the indicators for measuring them are poorly defined.
- Without sufficient trust between the payer and the pharmaceutical company, it will be difficult to make the agreement work successfully and conflict of interest may arise between them.
- It is not advisable to use them in treatments where the effects can only be seen in the long term, where there are no specific, objective or relevant response measures or where a control group cannot be formed.

In terms of practical experiences, it is worth mentioning that of the Catalan Institute of Oncology (ICO) which, since 2011, has implemented the PRS strategy from their management model and medicine policy (Calle et al., 2014) in line with that developed by CatSalut. The results are that, since 2011, the ICO has already signed 19 agreements for 9 oncological illnesses and included follow-up results for more than 1,600 patients.

The ICO published the first evaluation of a PRS agreement signed in Spain (Clopés et al., 2017). The main conclusions are that the clinical results under the PRS have managed to equal the results of the pivotal clinical trial and achieve certain economic profit on the cost of treatment. But the most important conclusion draws from the intangibles, because the strategy has made it possible to align professionals, funders and suppliers towards results and guide them towards the protocolised use of medicines, according to the criteria outlined in the agreement, which are those based on evidence.

Ultimately, the potential impact of the PRS, from the perspective of outlining the usage conditions of therapeutics, can have a much greater economic relevance than that of failures themselves. It is reasonable to believe that aligning all agents (manufacturer, payer and professionals) in the same direction in terms of use and the link with results incorporates incentives for optimising therapy and its efficient application. ■

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