Efficiency ratio and rocketing drug prices: old concerns and new possibilities

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Extremely high prices, limited benefits

One of the most significant phenomena in the recent years concerning the pharmaceutical industry and, at the same time, payers in healthcare systems, is the sharp acceleration in the growth of new drug prices [1].

Sustainability is being discussed across the board and every healthcare system deals with it in different ways, in particular pricing and reimbursement mechanisms.

Taking an example from oncology, representing one of the therapeutic areas where this unchecked growth is most evident, there were 69 cancer treatments available in the UK before the year 2000. Between 1995–1999 and 2010–2014, the median duration of treatment with new drugs increased from 181 to 263 days. The average cost per treatment rose from £3036 (equivalent to 20.6% of UK GDP per capita) to £20,233 (89% of GDP per capita) between 2005 and 2009, increasing to £35,383 (141.7% of GDP per capita) between 2010 and 2014 [2].

From the outset, this unprecedented increase in drug prices has been accompanied over time by the recognition of therapeutic benefits and, above all, by the justification of high investment in research and development, not forgetting, of course, the attribution of high prices for scientifically complex and innovative solutions.

While some new drugs are very effective, to the point of being considered innovations, many others do not present significant advantages over the drugs that are already available. However, new drugs usually have higher prices,

seemingly being justified by novelty value, rather than innovativeness. In recent years, a somewhat limited increase in efficacy has, therefore, been recorded, except in rare cases, corresponding to a generalised increase in drug prices, which immediately translates into higher costs being incurred by the healthcare system to treat a given disease.

Contrary to what one might expect, it was not us economists who raised the alarm about the rising prices of drugs, but oncologists, and not in Europe, where there is undoubtedly greater sensitivity towards health spending, given the prevalence of public systems, but in the United States, the country with the highest share of private spending.

In the country where drugs have always cost more than anywhere else in the world, some American oncologists realized that the soaring prices were beginning to be unexpectedly exaggerated, especially taking into account how, in most cases, the increases were not being justified by a proportionate increase in the effectiveness and safety of the drugs themselves [3, 4].

The way to verify how reasonable the price of a drug (or a treatment cost) is, is to relate it to the benefit it promises. First of all, with regard to benefits, the prices of oncological drugs are rising, but not in proportion to overall survival or “progression-free survival” rates (progression-free survival, or “PFS”, refers to the period of time during which the patient does not experience a worsening of the disease, an indicator widely used when survival data are not available) [5]. The poor correlation between treatment costs and survival and PFS rates is clearly visible in the following figure [6].

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(Source: Mailankody and Prasad, 2015).

Moreover, no relationship has been found between the price of drugs and their value, measured according to two scales by ASCO-VF and ESMO-MCBS (these scales attribute the scores to some important characteristics of oncology drugs, such as increased survival, PFS and patients' quality of life) [7].

Another study [8] examined the 62 new cancer drugs approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the period 2003–2013 and analyzed the 53 evaluated by the British, French or Australian HTA (Healthcare Technology Assessment) agencies. Only 5% extended the overall survival of patients compared to the drugs already available at the beginning of the period, in 2003, and only by about 3.43 months on average. It was also reported that 45% of the

drugs (24 in total) had no survival data or no evidence of higher survival compared to existing drugs.

Surprisingly, the authorities that assess the safety and efficacy of new drugs granted approval to drugs that did not introduce improvements in efficacy, and it is equally as surprising that the institutions that are specifically responsible for funding expenditure on cancer drugs introduced poorly effective drugs in the first place. This is the case with the Cancer Drug Fund (CDF) in Great Britain. Of the 47 indications approved by the CDF in the period between 2010 and 2015, only 18 (38%) had statistically significant survival data, with a median gain of 3.1 months (from a minimum of 1.4 months to a maximum of 15.7 months) [9]. Using two clinical benefit scales (not only survival, but also quality of life and other clinical indicators), only 23 (48%) and nine (18%) met the criteria of the American Society of Clinical Oncology (ASCO) and the European Society of Medical

Oncology (ESMO) scales, respectively. It should be noted that NICE (UK National Institute for Health and Care Excellence), the agency that recommends NHS drugs in England and Wales, after careful assessment, had previously rejected 55% of these drugs because they did not meet the criteria of cost-effectiveness. This case unfortunately shows that, even when the criterion of cost-effectiveness plays such an important role, some oncological drugs offer little or no improvements in terms of efficacy and are very expensive: the authors of this study concluded, with more than a slight hint of bitterness, that the CDF had not delivered meaningful value to cancer patients.

Agencies like the FDA and EMA have approved drugs with insufficient evidence. Less than 50% of new drugs approved in the USA and in Europe present data on their comparative benefits and adverse effects compared with existing treatment options [10]. From 2009 to 2013, the EMA approved 48 oncological drugs for 68 indications, and in 35% of cases with a median OS of only 2.7 months, while the remaining indications did not show any survival gain [11]. Also in Canada, the cost of cancer drugs is increasing without any strong evidence of improved survival [12].

In the meantime, the quality of life and levels of safety offered by new drugs have improved over recent years, with some breakthrough new drugs entering the market, such as PDL-1 immunologic treatments for cancer.

Price dynamics, however, need to be changed even in cases where drugs bring great benefits to patients, because comparing costs to effectiveness is not enough when the number of patients being treated is so high and when excessive costs would quickly lead to the collapse of any health-care system.

How have payers managed the problem?

The main criteria adopted can be summarised as follows.

1. Use of budget impact models, justifying a reduction in the price requested by manufacturers; price demands are now very high, with the awareness that prices will be approved a little bit lower, but shall nonetheless remain high.
2. Use of confidential discounts. In this way, the ex-factory price remains quite homogeneous among the different countries, but lower net prices can be obtained.
3. Use of Managed Entry Agreements (MEAs), either financial agreements, like cost-sharing, or performance-based, like payment-for-performance; in practice, such agreements allow for a reduction in the average cost per patient.
4. Use of the efficiency criterion, as calculated by the incremental cost-effectiveness ratio (ICER).

5. Combination of cost-effectiveness and budget impact, mainly applying a ceiling, as is the case for expensive new treatments, such as CAR-T.
6. Application of internal restrictions by local payers (e.g. hospitals), based on tenders, special negotiations with pharmaceutical companies and also internal prescription rules based on the age of patients, comorbidities, etc.

However, as mentioned above, the growth in prices, even with reference to net prices, seems unstoppable. The cost-effectiveness criterion is mandatory in some countries and is applied as the dominant (if not the only) factor in the decision-making process, while in other regions this is only indicative and used as part of a multi-criteria approach. Nevertheless, the ICER is usually calculated and made publicly available for many technologies, as this is useful to understand the value-for-money of a new product.

The pitfalls of the ICER have been described and extensively commented on elsewhere, as have those of the QALY (quality adjusted life year), as health outcome measure; however, the ICER continues to be routinely calculated for the majority of new technologies, using QALY as a common outcome measure.

To make decisions on prices and reimbursements, health authorities must include some external factors such as the ICER threshold to decide whether a new technology will be authorised or not. This value of around €30,000 per QALY represents a political decision that triggers several direct consequences, with the most important one probably being the new drug being prescribed instead of other existing options, with the corresponding additional budget impact. It also has indirect consequences, such as continuous price rises despite rather small QALY increases. We believe that the latter indirect consequence has attracted less attention among policymakers and we would like to suggest some potential ways of mitigating its effects. By introducing an additional criterion to the ICER, price growth would slow down, while maintaining the possibility of rewarding new drugs that demonstrate reasonable increases in benefits with higher prices.

A new criterion for pricing and reimbursement

As we will look at in more detail in one of our next articles, the idea is to provide payers with a new ICER criterion (even those who do not use CEA could use it, at least as a reference: in any case, also Italy, France and Spain use ICERs under certain circumstances).

When applying cost-effectiveness analysis to evaluate a new drug, it is compared to other technology to estimate

the incremental cost increase and the incremental QALYs (for simplicity, we have excluded the case in which the new drug produces additional QALYs at a lower cost than the comparator, as this does not happen very often). Assuming that the ICER obtained in this way is within the threshold value, e.g. €30,000, the drug can be reimbursed at a higher price than the existing drug (the comparator). For simplicity, in this article, we are using an equivalence between the cost associated with the therapy and the price of the drug, even if other healthcare resources, such as hospitalisation, diagnostic tests, exams, etc., are also normally taken into account in the cost. However, it should be remembered that, for high-cost therapies, the price of the drug is the predominant cost component. Therefore, every new drug, even if it is only slightly more effective, brings with it a price increase. The next drug will produce a further increase, and so on. To slow down these progressive price increases, we suggest that the price premium determined by the increase in QALYs should only be applicable if there is a minimum increase in said QALYs.

Let p_0 be the price of the comparator and $p_1(\Delta q)$ be the price of the new cost-effective drug that brings about a QALY gain Δq . Let $\bar{q}$ be the minimum increase in QALYs. The price of the new drug would be determined as follows:

$$p_1(\Delta q) = \begin{cases} p_0, & \Delta q \leq \bar{q} \\ p_0 + 30,000(\Delta q - \bar{q}), & \Delta q > \bar{q} \end{cases}$$

For example, let us assume a minimum QALY gain of 0.5 as an additional new criterion. In this case, if drug B (new drug) aims a price per treatment of €70,000 and provides an incremental QALY of 0.4 compared to the comparator, which has a price of €60,000, drug B would get the same price as drug A. No price increase would therefore apply. If, on the other hand, the standard ICER criterion were applied, drug B would get the price of €70,000 because the ICER would be €25,000 < €30,000.

If drug B had a QALY gain of 0.6, the ICER would be calculated based on 0.1 QALYs, $(0.6 - 0.5 = 0.1)$ thus obtaining an ICER of €100,000, which would exceed the threshold of €30,000. In this case, the application of the ICER criterion would advise an acceptable price of €63,000 (to bring the ICER to €30,000).

Applying the normal ICER to the €10,000 desired price increase and 0.6 QALY gain, we would get a value of €16,667, which is largely acceptable, and at €78,000 absolute price an ICER of €30,000. Therefore, with the standard ICER, the price would increase from €60,000 to €78,000, while, with the new QALY threshold, it would increase from €60,000 to €63,000.

There are several aspects that we plan to consider in further research, including:

1. The choice of the minimum QALY gain, on which to base the ICER calculation, is subjective, as is notoriously the €30,000 threshold. Setting this gain at 0.5 is perhaps high, but we will show the possible simulations with different values. Initial estimations applied to certain therapeutic groups show that, by applying this new criterion, drug prices would be about 25–50% lower.
2. This new criterion might differ if it is applied to a new, first-in-class drug, or to a new drug that belongs to an existing class. For example, it can be assumed that the investment in R&D for the first and second PDL-1 inhibitor is higher than the investment in R&D for the following PDL-1 inhibitors. The first-in-class drugs would therefore see a less stringent application of the new criterion, to reward them with higher prices.
3. From an analytical perspective, it will be necessary to discuss the implications of this new method with respect to welfare theory, cost–benefit analysis in particular.

Final remarks

We understand that new products not only provide higher efficacy in terms of incremental overall survival or progression-free survival, but usually also have a better safety profile, which is not so easy and straightforward to incorporate into the QALY index. These latter elements must also be considered as potential advantages of new products. However, the major key point of new products is their efficacy that translates directly to QALY gain. If this value is not too high, as it seems to be the case with many of the products described above, the calculation of both the ICER and the threshold criterion lead to continuous price increases, which we have observed even in ICER jurisdictions.

In spite of the technical difficulties related to the calculation of the ICER, this instrument does end up producing a figure that reflects the value of the new technology. Some jurisdictions then use this data as a dominant factor to fix prices and orientate prescriptions, others as another element in a multi-criteria decision-making process related to the adoption of new technologies. Nevertheless, this ICER data per se is not enough to make the decision, unless it is combined with a political criterion, commonly the acceptance-rejection threshold. The way this threshold is established has received attention, unlike its consequences in terms of price dynamics. We must emphasize the necessity of supplementing the ICER threshold with a new criterion based on a QALY threshold, aiming to reduce the pressure of price increases. This threshold should be based on what society considers as a meaningful departure from the QALYs, already achieved by other health technologies, and would hopefully help to visualize the requested value of new products. If this were the case, then price increases would

presumably be lower in the coming years, helping public health systems to cope with the sustainability challenges they face, while still maintaining incentives to develop new drugs.

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