Application of the Price–Volume Approach in Cases of Innovative Drugs Where Value-Based Pricing is Inadequate: Description of Real Experiences in Italy

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Abstract Several cases of expensive drugs designed for large patient populations (e.g. sofosbuvir) have raised a complex question in terms of drug pricing. Even assuming value-based pricing, the treatment with these drugs of all eligible patients would have an immense budgetary impact, which is unsustainable also for the richest countries. This raises the need to reduce the prices of these agents in comparison with those suggested by the value-based approach and to devise new pricing methods that can achieve this goal. The present study discusses in detail the following two methods: (i) The approach based on setting nation-wide budget thresholds for individual innovative agents in which a fixed proportion of the historical pharmaceutical expenditure represents the maximum budget attributable to an innovative treatment; (ii) The approach based on nation-wide price–volume agreements in which drug prices are progressively reduced as more patients receive the treatment. The first approach has been developed in the USA by the Institute for Clinical and Economic Review and has been applied to PCSK9 inhibitors (alirocumab and evolocumab). The second approach has been designed for the Italian market and has found a systematic application to manage the price of ranibizumab, sofosbuvir, and PCSK9 inhibitors. While, in the past, price–volume agreements have been applied only on an empirical basis (i.e. in the absence of any quantitative theoretical rule), more recently some explicit mathematical models have been described. The performance of these models is now being evaluated on the basis of the real-world experiences conducted in some European countries, especially Italy.

Key Points

- Value-based prices of innovative drugs are generally lower than those claimed by pharmaceutical companies.
- The pricing method approach based on setting nation-wide budget thresholds for individual innovative agents represents an important advantage in a field where most historical approaches of governance have been fully empirical.
- The pricing method approach based on nation-wide price-volume agreements in which drug prices are progressively reduced as more patients receive the treatment has a crucial role in promoting the sustainability of these critical treatments.

1 Introduction

Value-based prices of innovative drugs are generally lower than those claimed by pharmaceutical companies, and so their application improves health-care sustainability [1, 2]. For this reason, numerous countries have faced the issue of reducing list prices of innovative drugs to value-based prices, with varying success [3, 4]. While this progressive application of value-based pricing is ongoing, several cases of expensive drugs designed for large patient populations (e.g. sofosbuvir [5] and PCSK9 inhibitors [6–11]) have raised another more complex question. For these drugs,
even assuming value-based pricing, the treatment of all eligible patients would have an immense budgetary impact [5, 6] unsustainable even for the richest countries.

One solution is to devise original techniques that reduce drug prices in comparison with the value-based approach, but ensure at the same time that these prices are acceptable for drug companies.

The present study was aimed at exploring “real cases” of application of these non-value-based techniques and was focused on two methods that already have a reasonable degree of applicability:

1. The approach based on setting nation-wide budget thresholds for individual innovative agents [7–11], in which a fixed proportion of the historical pharmaceutical expenditure represents the maximum budget attributable to an innovative treatment. According to this approach, as many patients as possible are treated provided that the overall expenditure does not exceed the pre-defined threshold. Clearly, lower prices allow more patients to be treated.

2. The approach based on nation-wide price–volume agreements (applied quite extensively in Italy) [12–14] in which drug prices are progressively reduced as more patients receive the treatment.

On the other hand, this paper does not describe the value-based approach, but makes reference to the vast literature published on this topic [15–23] especially work in the UK, much of which was published after the Office of Fair Trading (OFT) report in 2007 [23].

2 Approach Based on Nation-Wide Budget Thresholds for Individual Innovative Agents

This approach [7–11] has been developed in the USA by the Consultancy Institute called ICER (Institute for Clinical and Economic Review) and was initially designed to manage the price of PCSK9 inhibitors (alirocumab and evolocumab) at their launch on the US market. Although its application has only been described for these two agents, this method has a general validity.

In the second semester of 2015, the first analysis [7, 8] conducted by ICER on PCSK9 inhibitors was a traditional cost-effectiveness evaluation that estimated a yearly maximum cost per patient of US$3166, US$5404, and US$7735 according to thresholds of US$50,000, US$100,000, and US$150,000 per QALY gained, respectively. While these prices were determined through the “traditional” value-based approach, their values were nonetheless thought to be too high. This is because of the extremely large population potentially treatable with PCSK9 inhibitors (up to 2.6 million in the USA), making the budget impact unsustainable under these conditions.

The need to set the price for evolocumab and alirocumab at levels lower than the value-based estimates was therefore explicitly recognised [7–11], and the question was successfully addressed by a “new math” developed by ICER [11]. This new-math relies on the following rationale [7–11]: the overall budget for these agents should not exceed “the amount of net cost increase per individual new intervention that would contribute to growth in overall health care spending greater than the anticipated growth in national GDP + 1%”. According to this criterion, an annual price of US$2177 per patient was calculated for each PCSK9 inhibitor. The full report, published at the end of 2015 [9], provides a detailed description of this method, which unfortunately is quite complex in operational terms. The most critical steps that, in the case of PCSK9 inhibitors, led to the estimation of the annual cost of US$2177 per patient are described in detail elsewhere [10].

The main strength in employing a nation-wide budget threshold lies in its rational nature that represents an important advantage in a field where most historical approaches of governance have been fully empirical. Its main limitation is that, despite its theoretical appeal, no applications have yet taken place in the context of a public jurisdiction, but there are only a few examples managed essentially as a scientific exercise. It seems that this method is sound, but its undoubted complexity is an important drawback limiting its application. Another potential weakness is that there is a quite uncertain limit between handling a pharmacological class as a whole and handling separately the individual agents of the same class; in this latter case, the overall budget is in fact increased in proportion to the number of available drugs although the patient population is likely to remain unchanged.

3 Approach Based on Nation-Wide Exponential Price–Volume Agreements

More recently, other mathematical approaches designed for the Italian market have been proposed to manage the price of expensive, innovative drugs that involve large patient populations [12–14]. These preliminary experiences were focused on ranibizumab [12, 13], sofosbuvir [12, 13], and PCSK9 inhibitors [14].

The basic assumption of this method lies in the price–volume relationship in which the price undergoes an exponential decay as more patients are being treated [12–14]. The basic parameter of the model is represented by the price halving population (PHP) according to which the treatment price is halved at every increase of the treated patients equal to PHP. Two variants of this method are
available: the first relies on a continuous decay function while the second adopts a discrete series of progressive price rebates (with downward adjustments when every predefined volume of sales is achieved). Only the first variant is taken in consideration in the present article.

Thus far, the analyses based on the exponential method have yielded the following results: prices are halved for ranibizumab at every increase of 41,878 treated patients (expected population = 20,000 patients) [12, 13], for sofosbuvir at every increase of 18,579 treated patients (expected population = 60,000 patients) [12, 13], and for evolocumab or alirocumab at every increase of 25,000 treated patients (expected population = 50,000 or 100,000 patients; see Fig. 1, panel a) [14]. The average price was estimated to be EUR7705 to treat 20,000 patients (or EUR6157 to treat 50,000 patients) with ranibizumab, EUR14,969 to treat 60,000 patients with sofosbuvir, and EUR3382 to treat 100,000 patients (or EUR5411 to treat 50,000 patients) with a PCSK9 inhibitor. Interestingly enough, the treatment cost per patient per year for PCSK9 inhibitors reduced to less than EUR626 at more than 100,000 treated patients.

It should be noted that in Italy, the analyses for ranibizumab and sofosbuvir have already translated into specific nation-wide reimbursement decisions made by the Italian Drug Agency (AIFA). In contrast, the model designed for PCSK9 inhibitors is still at a stage of a scientific report, although the reimbursement decision on these agents is shortly expected.

This approach in which the values of PHP can be different across different drugs allows us to individualise the price decisions for drugs that have different characteristics. However, it is noteworthy that, in quantitative terms, also other factors might be implicated as well. However, some important clues are pinpointed by the data presented in Fig. 1, panel a.

In the application of this method, some questions have found a rational response, while others are still open. For example, why did the Italian decision-makers empirically establish a more rapid price decay for sofosbuvir than for ranibizumab? The answer is that the sustainability of sofosbuvir is more critical than that of ranibizumab. In fact, the values of yearly NwBI for these agents (calculated at model-predicted average prices) differ considerably.

![Fig. 1](imageurl)
between these two agents: for ranibizumab at 20,000 patients: NWBI = EUR181 million at an average price of EUR7705; for ranibizumab at 50,000 patients: NWBI = EUR308 million at an average price of EUR6157; for sofosbuvir at 60,000 patients: NWBI = EUR2250 million at an average price of EUR14,969. It can be seen that, unlike ranibizumab, sofosbuvir has a very high cost per patient and is potentially indicated for a very large patient population; this drug therefore requires a more aggressive policy to limit its cost. In other words, agents with very strong budget impact like sofosbuvir must be managed by imposing a very rapid price decay in the price–volume relationship. In contrast, drugs like ranibizumab are much less critical, and so their price decay with volume can be set according to a less aggressive relationship.

As regards the main limitations of this approach, one problem is that the parameters modelling the price decay (PHP and NWBI) depend on the number of inhabitants of the country concerned. Hence, one limit of the exponential model is that all of the analyses described herein referred to the pharmaceutical market of a country of 60 million people (like Italy); therefore, the application of this same approach to other countries will obviously require some adaptations.

In managing this method, we encountered—as expected—serious problems in terms of information availability, firstly because the material on this topic is scanty and secondly because most of the local agreements are strictly confidential. Despite these problems, in the two real cases examined in some detail (ranibizumab in macular degeneration and sofosbuvir in hepatitis C) we retrieved from various sources the minimum information needed to run the model. More importantly, our results were quite satisfactory because, in both of these real examples, the experimental data (i.e. the data pairs of y-vs-x) could be fitted successfully to the respective models.

4 Discussion and Conclusion

The issue of drug prices is extremely complex covering a vast literature and so, to avoid an excessive length of this paper and an excessive complexity, our article was focused on a limited number of topics. In particular, the main focus included some experiences conducted in Italy in the field of drug pricing. It should be recalled that value-based pricing has received a poor formal acceptance in Italy. Although this approach has been used quite frequently for national drug pricing, its theory is not generally recognised by the Italian medicines agency and therefore the application of the value-based approach typically is implicit rather than explicit. On the other hand, a number of other methods of pharmaceutical governance, specific to the Italian scenario, have been developed and put into practice, which represent a positive peculiarity of the pharmaceutical governance in Italy. These methods include indication-specific drug pricing, paybacks by drug companies related to cases of therapeutic failures (i.e. the payment by results approach), implementation of national patient-based registries to monitor innovative drugs and to manage their real-world effectiveness. The application of the price–volume approach has been discussed in detail in this paper, while the other techniques have been examined and discussed elsewhere [4].

The issue of health opportunity costs [24–28] influences all of these pricing techniques because the assessment of opportunity costs provides the link between affordability and cost effectiveness. As pointed out by Karlsberg Schaffer et al. [24], identifying what, in practice, is foregone when new cost-increasing technologies are introduced is important for understanding the effects of health technology assessment decisions on the NHS or any other health-care system. Opportunity cost, or benefits forgone, measured in terms of utility by using resources in one way rather than another also represent the economic and equity rationale for carrying out budget-impact analyses. In other words, by choosing to draw down the budget in one way, decision-makers forgo other opportunities to use the same resources. For this reason, budget-impact analysis is more useful to the decision-maker than cost-effectiveness analysis if the objective is not to maximise health gains subject to a budget or resource constraint, but to reduce variance in health gains.

Ireland represents an interesting exception to the rule whereby opportunity costs are disregarded in the context of drug pricing. As pointed out by O’Mahony and Coughlan [28], after setting the cost effectiveness threshold at EUR45,000/quality-adjusted life-year (QALY) in substitution for the previously unofficial threshold of EUR20,000/QALY, drugs within this threshold were granted reimbursement, but it appeared that the threshold resembled a price floor rather than a ceiling. The aforementioned Irish threshold for cost effectiveness was probably too high given recent estimates of a threshold for the UK based on the cost effectiveness of services forgone of approximately GBP13,000/QALY and so an excessive threshold risks causing the Irish health system unintended harm. More recently, Irish legislation defined cost effectiveness in terms of the opportunity cost of services forgone when choosing what threshold to apply.

Unfortunately, opportunity costs are often neglected by the organisms responsible for negotiating drug pricing. In the UK, Karlsberg Schaffer et al. [24] have pointed out that service displacements are not linkable to particular NICE technology appraisals and there appears to be a general lack of explicit prioritisation activities.
Our final comments are focused on the strengths and the limitations of the present article. Price–volume agreements have always been applied in the past on an empirical basis, i.e. in the absence of any quantitative theoretical rule. The experiences described in this article are a first attempt to develop a more sound theoretical and practical framework in this field. As regards the limitations, we recognise that we have discussed especially the point of view of payers while the perspective of industry has not been considered.

Compliance with Ethical Standards

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Conflict of interest
A. Messori has no conflicts of interest to declare.

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