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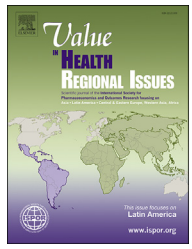

Brief Report

The Price of Substitute Technologies

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ABSTRACT

Background: Only a small share of new drugs is truly innovative; 85% to 90% of all new health technologies have little or no advantage over existing therapeutic alternatives. Health economic evaluations can be used to induce acceptable prices for new technologies through threshold pricing. **Objective:** This work discusses a cost-effectiveness threshold (λ) to be applied to the price regulation of substitute technologies. **Methods:** Considering that substitute technologies add only small marginal benefits in terms of innovation or ethical considerations to the system, it does not make sense to allow a loss of efficiency to list them. It has been postulated that the threshold calculated from opportunity costs (κ) represents its maximum possible value and that there must be a threshold (β) that maximizes consumer surplus. For a substitute technology to be listed, the cost of treatment associated with it must be lower than the cost of treatment of the incumbent technology added to the difference in effectiveness priced at the threshold. **Results:** There is no reason for us to believe that the oligopolistic pharmaceutical market is currently charging prices at the cost of production. That way, the cost-effectiveness ratio of the incumbent technology, when lower than κ, is shown through a deductive process to be a plausible estimate for λ that fulfills the objective of maximizing consumer benefit, granting producers a part of the combined surplus to stimulate research and development; that is, it would be between β and κ. **Conclusion:** In conclusion, the price of substitute technologies should be limited by the cost-effectiveness ratio of the incumbent technology.

Keywords: cost-effectiveness analysis, cost-benefit analysis, health technology assessment, cost-effectiveness thresholds, health economics

Introduction

One important objective of price regulation in the drug market is to find an optimal trade-off between incentives for research and development (R&D), consumer protection, and value for money.[1,2] It has been suggested that higher price levels are associated with higher investments in R&D.[3] Nevertheless, there is still a need to improve access to new technologies and to guarantee that they provide more health benefits than they displace in consequence of their costs.[4-7] In some countries, prices are determined by an international benchmarking approach, which uses the price of the same technology in other countries as a reference.[8] Pharmaceutical companies can also use the price of other technologies that have already been approved for the same indication to induce higher prices for their products.[9] This approach, known as reference pricing, has led to progressive cost increases for several drugs over the years.[10-13] In Brazil, for instance, trastuzumab and pertuzumab for metastatic HER-2+ breast cancer were incorporated in the Unified Health System with a low value for money.[14,15] None of these methods, however, links the price of new technologies to an objective estimate of value.

Health economic evaluations can be used to determine acceptable prices for the incorporation of new technologies through *threshold pricing*. The result of a cost-effectiveness

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analysis is usually assessed through the cost-effectiveness ratio (CER), calculated as total cost divided by total effectiveness, and the incremental cost-effectiveness ratio (ICER), calculated as the difference in total cost divided by the difference in total effectiveness between therapeutic alternatives.[16-18] In the absence of dominance, the ICER is insufficient to provide a recommendation: for new technologies to be recommended, the ICER must be compared to a critical ratio, the cost-effectiveness threshold (λ), which represents the maximum acceptable cost for an extra unit of benefit.[19-24] Through threshold pricing, the price of a technology is set to the maximum possible value for the product to be cost-effective when compared with a defined λ. Therefore, when λ is set above the potential value for a context with scarcity, it allows pharmaceutical companies to demand higher prices for new technologies.[4,25-27] Although there are various methods to calculate λ, and most of the literature adopts the perspective of demand,[5,24] the definition of the threshold based on a supply-side approach is considered ideal by many important authors.[6,7,28-30]

Threshold pricing is closely linked to value-based pricing (VBP). Conceptually, value-based schemes link the price of a technology to its benefits rather than its production costs.[1,5,8,31] From a supply-side perspective, VBP should ensure that technologies are recommended for incorporation only at prices at which net health benefits are positive (ie, when health benefits exceed health losses owing to the extra costs incurred). In other words, the maximum price of a technology is determined by the comparison between the ICER and the threshold defined by opportunity costs (κ, the shadow price of a unit of effectiveness).[32] When ICER $<$ κ, the entrant technology would be providing more health benefits than it would be displacing on average.[6,7] The application of VBP implies a tendency not to accept high prices for technologies that do not prove sufficient value, compared with the existing alternatives, through valid and transparent methods.[8,21,25,33] When the price of a technology is strategically chosen to suit κ, VBP ensures that the maximum acceptable price is being paid for the technology, so the surplus is fully absorbed by the producers and there are no net health gains for consumers.[1,4,34] It is expected that producers will adopt a strategic behavior and define threshold prices to maximize their profit. Nevertheless, recommendations based on a well-established λ may influence companies to voluntarily lower their prices to improve the chance of incorporation[4,5,35]; that is, the companies might be willing to reduce prices so that their technologies can be cost-effective and considered for incorporation in the health system.

An important aspect related to the introduction of new technologies is their additional benefits. Only a small share of new drugs are truly innovative; 85% to 90% of all innovations have little or no advantage over existing therapeutic alternatives.[33,36-39] Conceptually, "me-too" or "follow-on" drugs are new entrants in a therapeutic class that has been defined by an innovative drug or a drug with the same mechanism of action.[36,40-42] Critics argue that me-too drugs add little or no value to the therapeutic arsenal, make clinical decisions more difficult, increase healthcare costs, and waste billions of dollars annually on marketing and advertising, which could be better spent on R&D of orphan drugs. On the other hand, the possibility of substitution creates competition in the pharmaceutical market and may drive improvements in safety, efficacy, and effectiveness as well as a reduction in the costs associated with a particular class of drugs. Because the effects of many drugs can vary among patients, the registration of several drugs of the same class may improve the adequacy of the pharmacotherapy at the individual level.[36,40,41,43-46]

Simply stated, substitutes are goods that serve the same purpose.[47] Under VBP, substitute technologies, such as me-too drugs, are valued according to the price of other drugs in the same class.[26] The first product in a new class determines the base price, and the next should offer better benefits or a lower total cost of treatment to justify incorporation.[45] In the United States, new molecules that do not have a significant advantage over older drugs in the same class tend to be marketed at lower prices, and drugs that show therapeutic advantage over the existing treatment enter the market at higher prices, confirming the existence of a relationship between the clinical benefit and the price of medicines.[48] The arrival of generic drugs causes a downward trend in prices of reference and me-too drugs.[26] The registration of me-too drugs, especially the ones obtained from minor modifications in already known molecules, is one of the unofficial methods of "ever-greening," situations in which companies extend their monopoly by exploring loopholes in patent laws.[49] When the protection period of a patent is about to end, companies might register me-too drugs to substitute older drugs and ensure their profit after generic medicines arrive at the market. This strategy is sometimes called "brand migration".[49] Evidence shows that in the United States, in 2013, the selection of generic omeprazole over Nexium and generic atorvastatin over Crestor would have represented savings of $870 million and $1.203 billion, respectively.[50]

Many countries still struggle with the definition of prices for the incorporation of new medical products in their health systems. In this context, the objective of this article is to demonstrate a threshold for theoretical substitute technologies. The results presented can help regulators calculate the maximum acceptable price for the incorporation of substitute technologies in the health system.

Modified Cost-Effectiveness Threshold for Me-Too Drug Pricing

Assuming that the healthcare budget is spent to maximize health, a new technology would be listed only when the expected net health benefit (NHBe) is at least as large as the initial net health benefit (NHBo) before the incorporation of the entrant technology (NHBe $-$ NHBo $\geq$ 0). As previously discussed, the maximum acceptable price for the incorporation of any technology should occur when ICER $=$ λ $=$ κ because the cost of treatment is a function of the price of the technologies [C $=$ f(p)]. If any price above that is established, the system would be paying more for a technology than it is worth.[1,4,7,26,51] In addition, there would be a theoretical β threshold that makes a technology available at the economic cost; that is, the price that compensates for the costs of production so that the company may remain in the market, the break-even price.[52] For a technology to be listed, the ICER should be lower than the threshold; that is, the restriction ICER $\leq$ λ must be valid (equation 1).

$$\frac{C_E - C_I}{E_E - E_I} \leq \lambda \quad (1)$$

where C_E and C_I are the cost of treatment and E_E and E_I are the effectiveness of the entrant (substitute) and incumbent technology, respectively. Rearranging this inequality, we have that

$$C_E - C_I \leq \Delta E\lambda \quad (2)$$

$$C_E \leq C_I + \Delta E\lambda \quad (3)$$

Therefore, according to equation 3, λ values the difference in effectiveness between technologies; that is, λ determines how much higher the cost of treatment of an entrant technology can be

because of its incremental effectiveness. Substituting ΔE for $E_E - E_I$ and C_I for $E_I(CER_I)$, as expressed by the definition $CER_I = \frac{C_I}{E_I}$, it can be shown that the maximum cost of treatment with an entrant technology must be

$$C_E \leq E_I(CER_I) + E_E\lambda - E_I\lambda \quad (4)$$

$$C_E \leq E_E\lambda + E(CER_I - \lambda) \quad (5)$$

in which CER_I is the cost-effectiveness ratio of the incumbent, an estimative of its efficiency. The lower the efficiency of the incumbent, and the higher the threshold, the higher the market price of an entrant technology could be. Dividing equation 5 by E_E, it can be shown that

$$CER_E \leq \frac{E_I}{E_E}(CER_I - \lambda) + \lambda \quad (6)$$

Considering equation 6, and assuming that most entrant technologies are more effective than the listed comparators,[33,53] 2 results may follow:

Result 1: The cost-effectiveness ratio of the entrant technology can only be higher than the cost-effectiveness ratio of the incumbent when the cost-effectiveness ratio of the incumbent is lower than the threshold.

$CER_E > CER_I$ *only if* $CER_I < \lambda$

Result 2: If the cost-effectiveness ratio of the incumbent is higher than the threshold, then the cost-effectiveness ratio of the entrant technology must be lower than the cost-effectiveness ratio of the incumbent.

if $CER_I > \lambda$, then it is mandatory that $CER_E < CER_I$.

In general, achieving economic efficiency is equivalent to maximizing value for money.[19,54,55] According to result 2 and the definition of κ (ie, the value of λ that zeros consumer surplus, the shadow price of a unit of effectiveness), when $CER_I > \kappa$ then $CER_E < CER_I$ is a *sine qua non* condition to maximization. It is not to be expected that any technology would be priced at the economic cost in an oligopolistic pharmaceutical market, so the *CER* should commonly be higher than β. Because β is the value of λ that makes a technology available at the break-even price and the maximum value of λ is κ, a CER_I less than κ is between β and κ. Therefore, although the threshold could be mathematically higher than the CER_I as shown in result 1, in this scenario, the CER_I is a plausible estimate for the threshold because it fulfills the objective of maximizing the consumer net benefit, granting producers a part of the combined surplus to stimulate R&D. It would ensure that the marginal extra effectiveness in a context with no improvements in equity and innovation would be valued at the same rate as the effectiveness of the incumbent: $C_E \leq E_E(CER_I)$. The proof of results 1 and 2 can be found in Appendix Aand B of the Supplementary Materials found at https://doi.org/10.1016/j.vhri.2019.08.474.

Discussion

The concepts presented in this article have practical relevance and evidence. Brazil, for example, has no explicit cost-effectiveness threshold to support a recommendation. Nevertheless, mentions of 1 to 3 GDP per capita/quality-adjusted life-year (QALY) are very common in the literature.[21,24,56,57] The maximum total cost of treatment with a hypothetical drug B ($E_B = 10.1$ QALY), substitute to a hypothetical drug A ($C_A = \$100.00$; $E_A = 10$ QALY), could be up to $3046.42 when the threshold is set at 3 GDP per capita/QALY and $101.00 if the cost-effective ratio of the incumbent is used as the threshold (see the demonstration in Appendix C of the Supplementary Materials found at https://doi.org/10.1016/j.vhri.2019.08.474). That is, for sure, a very aggressive example, but real examples of this effect can be found. In Brazil, olanzapine, risperidone, chlorpromazine, haloperidol, quetiapine, and ziprasidone are recommended as potential candidates for the first-line treatment of schizophrenia.[58] It has been shown that all oral antipsychotics are me-too drugs with no greater benefits in terms of treatment scheme or ethical relevance and innovation. They offer only small marginal improvements in efficacy or safety.[59-63] Santos[64] recently evaluated the cost-effectiveness of these drugs in Brazil. He observed that olanzapine is the most cost-effective drug in the system according to 6 previously described threshold values. Nevertheless, olanzapine was not the most efficient drug—chlorpromazine was. If a restriction that olanzapine has to be at least as efficient as chlorpromazine was applied, then olanzapine could cost up to ~$0.031/mg, and it would still be considered cost-effective. This price seems to be viable because there are purchase prices lower than this reported in the Health Price Bank database.[64] If the threshold was set at 3 GDP per capita/QALY, the price of olanzapine could be up to $0.745/mg when compared with chlorpromazine only or ~$0.350/mg, considering the full model, to be considered cost-effective.

Our approach keeps some similarities with the IQWiG's Efficiency Frontier but with a very different recommendation. Under their approach, all interventions for a specific condition are plotted in a cost-effectiveness plane, and the threshold for a new intervention is formed as an extension of the ICER between the 2 existing most effective technologies.[24,65-69] We, as IQWiG, applied an approach that privileges efficiency and focus on well-defined therapeutic areas, not setting priorities across the system.[24,67] Nevertheless, we recommended the use of the CER_I as the threshold in cases in which it is lower than κ and the technology being evaluated is a substitute. Also, IQWiG's economic evaluations consider only technologies judged to be superior on the benefit analysis,[67] raising an issue with the impossibility of funding less effective technologies even if they are cheaper. We do not recommend this restriction.

This method seems very restrictive at first, but as we reflect on its implications, we realize that it does not make sense to allow a loss of efficiency to list substitute technologies. This method is not adequate to evaluate drugs that provide ethical or innovation benefits to the system. The willingness to pay of the system for a drug that initiates a new therapeutic class is higher for innovative reasons, for example. There are unknown effects on the progress of science and new treatment possibilities for patients who are intolerant or unresponsive to other drug classes. In addition, drugs that might include previously untreated patients, facilitate administration, or improve adherence might deserve a better return on investment. New drugs that are not thermolabile or that are administered through a more convenient route or therapeutic scheme (eg, oral administration instead of subcutaneous, once daily instead of 3 times a day) would fall in this category. The method to determine when the CER_I is a good proxy for λ implies the knowledge of κ, which is not easy to calculate. Nevertheless, some estimates of κ exist for many countries, including Brazil.[30,70]

Transparency in price regulation is beneficial to pharmaceutical companies and consumers who become aware of the market rules and know what is to be expected when a new drug is launched into the market.[24] We demonstrated from basic concepts of pharmacoeconomics that the cost-effectiveness ratio of the incumbent technology should be used as the threshold to inform pricing decisions for substitute technologies that do not contribute to the system with equity or innovation. There are some foreseeable implications of adopting this parameter. Because competition tends to reduce treatment prices, there would be little incentive for producers to invest in areas that already have many representatives. Companies that already have listed drugs would have an incentive to reduce their price when

new competitors enter the market to avoid the loss of market share. It seems logical that companies would prefer to invest in areas with low efficiency and orphan diseases because they would have the possibility of charging higher prices, possibly bringing more benefits to consumers.

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Supplemental Material

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