Commentaries

Implementation of Value-based Pricing for Medicines

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ABSTRACT

Value-based pricing (VBP) is well established in markets for common goods and services, but wide consensus on VBP for pharmaceuticals is lacking. In principle, VBP implies that prices are mainly driven by a drug's value (value for money) and that the impact on budget (sustainability) is a second-order driver of price regulation. Although the literature provides descriptive analyses on regulations governing medicine price negotiation, there are few insights on whether and how price negotiation regulations have been implemented. The goal of this article was to cover this information gap for 5 European countries and the United States. VBP has been applied according to two models: (1) direct models in which cost-effectiveness is a driver; and (2) indirect, multi-attribute models characterized by greater discretion on the integration between the different value domains and the evaluation of consistency between costs and value. In these models, cost-effectiveness is not a driver. In addition, it is hard to evaluate within these models the actual implementation of VBP. Identifying whether and how VBP is applied requires a clear predefined link between added value and the premium price, as well as transparency in the way added value is converted into a premium price. In general, for these countries, it remains difficult to determine whether pricing is mostly driven by value (value-for-money) or impact on budget (sustainability). In instances in which thresholds on the incremental cost-effectiveness ratio are used, it becomes easier to understand whether VBP has been implemented. If VBP relies on a multi-criteria approach, greater transparency on which criteria have been used to assess a new drug and how they have been converted into a reasonable price may help in understanding whether a value-based approach has been used. (*Clin Ther*. 2020;42:15–24)

Keywords: Medicines, Value-based pricing, Regulation, Incremental cost-effectiveness ratio, Multi criteria decision analysis.

INTRODUCTION

Value-based pricing (VBP) is a well-established pricing method for goods and services. VBP dictates that the price of the commodity should reflect the value to the buyer rather than the actual costs of production augmented by the profit margin.[1] In principle, VBP for drugs means that prices charged to third payers are mainly linked to the drug's value and that impact on budget is a second-order driver of price regulation.[2] Combined with an appropriate mix of volumes that favors cheaper medicines among those that are considered interchangeable, VBP helps to maximize value within the available budget. However, although VBP for pharmaceuticals has been for years considered superior compared with cost-plus methods of price determination, it exhibits heterogeneous understanding on its meaning (what is value?),[3] aim (why use VBP),[4] and its conversion into price models. As a result, the translation of VBP into practice varies considerably across countries.

From an operational viewpoint, VBP first requires that a value framework be defined and systematically adopted (Figure 1). More specifically, a value framework requires that the relevant components of value (benefits) are: (1) identified (eg, unmet needs,

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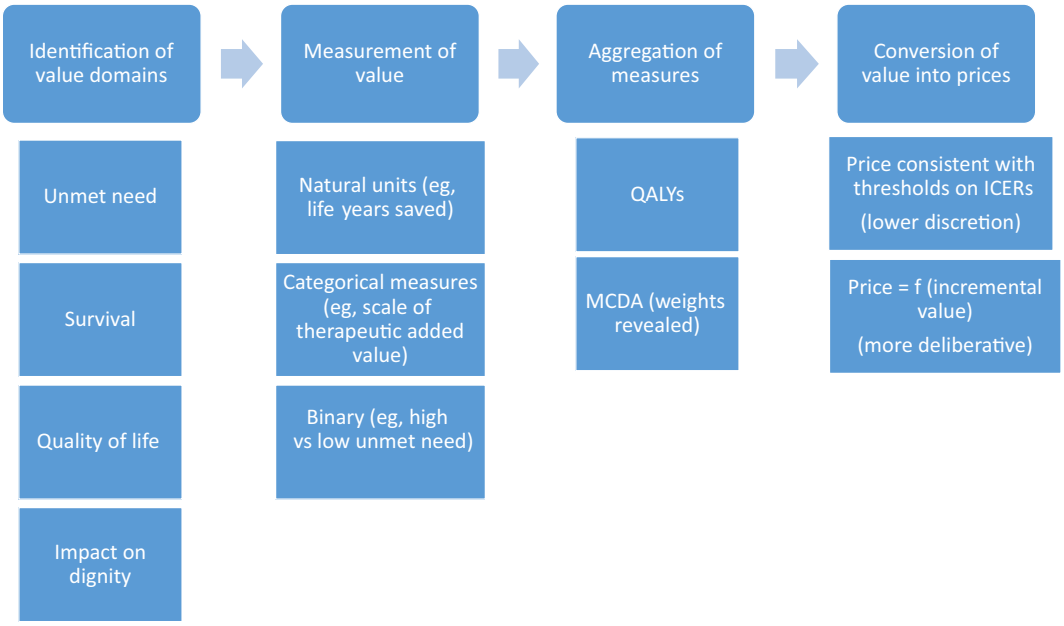

Figure 1. Operational steps for value-based pricing. ICER = incremental cost-effectiveness ratio; MCDA = multi-criteria decision analysis; QALYs = quality-adjusted life years. Elaboration on Sussex et al[5].

survival, quality of life, impact on dignity); (2) measured, through natural units (eg, life years gained), categorical assessment (eg, point scale of additional therapeutic value), or binary description (ie, high vs low unmet need); and (3) aggregated (eg, using quality-adjusted life years [QALYs] gained or weights revealed by users and/or decision-makers, through a multi-criteria decision analysis approach).[5] As a second step, the aggregate value should be converted into a price through models. The conversion method depends on the drivers identified in the value framework. If cost-effectiveness is the driver, the price will be calculated by using the incremental cost-effectiveness ratio and the relevant willingness-to-pay (WTP) thresholds or the net monetary benefit.[6] Otherwise, a premium price over the active comparator is identified in proportion to the additional value.

VBP also implies that uncertainty on value be considered when prices are set. Outcome-based managed entry agreements (OB-MEAs), which are payments on the grounds of the benefit to patients in a real-world setting, could be implemented for this purpose, through either a population-based (ie, postmarketing study to verify the medicine's impact in real life) or a payment-by-result contract in which payers pay only for responder patients.[7] Medicines are also issued approvals for different indications. Indication-based pricing or OB-MEAs should be implemented if value differs across indications, as long as health care providers are able to track a medicine's use per indication.[8] Finally, VBP for medicines usually refers to the ex-factory price. Pharmacy and wholesaler remuneration is set by law and should reflect the value of the service they provide and not the intrinsic value of the drug.

VBP across major European nations has been variously implemented (Table I).[9–12] In England, QALYs and incremental cost-effectiveness ratio thresholds are the main drivers of National Institute for Health and Care Excellence (NICE) appraisals, which indirectly influence prices freely set by companies and possible MEAs. In France, Italy, and Spain, prices are negotiated on the basis of the drug's additional clinical value, among other elements. In France, the additional clinical value is graded according to 5 categories for price negotiation purposes: only medicines with moderate to high

Table I. Medicine price setting in 5 European countries.

Country	Negotiating Entity	Value Criteria	MEAs	Role of ICER	Indication-based Pricing
France	CEPS (CEESP for economic evaluation)	Additional clinical value (graded)	Mainly finance-based (price/volume agreements)	For moderate to high additional clinical value/budget impact more than €20 million	No
Germany	SHI (Discount)	Additional therapeutic value (graded)	—	In principle, an efficiency frontier	No
Italy	CPR-AIFA	Additional clinical value	Both finance-based and outcome-based	Suggested for "very innovative drugs" and medicines for orphan diseases	Yes, through MEAs
Spain	CIPM	Additional clinical value	Mainly finance-based	—	No
United Kingdom	DoH (MEAs)	QALYs	Mainly finance-based	Most important criterion	Yes, through MEAs

CEESP = Economic Evaluation and Public Health Committee; CEPS = Health Products Economic Committee; CIPM = Prices and Reimbursement Inter-ministerial Committee; CPR-AIFA = Price/Reimbursement Committee—National Medicines Agency; DoH = Department of Health; MEA = managed entry agreement; QALYs = quality-adjusted life years; SHI = Social Health Insurance.
Elaboration on Jommi and Minghetti,[9] Panteli et al,[10] Theidel and von der Schulenburg,[11] and Toumi et al.[12]

additional value can aspire to a price premium, provided that companies deliver a cost-effectiveness analysis if the expected budget impact is more than €20 million per year in the first 3 years. In Italy, the additional therapeutic value, along with the unmet need and the quality of the evidence, is graded to determine a medicine's "innovativeness status" (https://www.aifa.gov.it/farmaci-innovativi;last accessedOctober24, 2019): an innovative medicine is not necessarily granted a price premium, but it facilitates market access. In Germany, prices are set by industry, but for most medicines, a discount over list price is negotiated at maximum 1 year after market launch using various parameters, including the added therapeutic value (clinical value and quality of life), as stipulated by the country's 2011 Act on the Reform of the Market for Medical Products law (Amnog).

The literature provides descriptive analyses on the regulation of price negotiation and the formal adoption of a VBP approach. However, to the best of our knowledge, the evidence on whether this regulation has been implemented has not been reviewed thus far. The aim of the present article was to cover this information gap. The following section illustates the evidence from the United Kingdom, where VBP mainly relies on QALYs as an aggregate measure of value and incremental cost-effectiveness ratio thresholds as a way of converting value into VBP. The third section focuses on France, Germany, Italy, and Spain, where cost-effectiveness is not (or not systematically) used for medicines pricing. The fourth section illustrates the application of VBP in one country, the United States, where prices are freely set by industry. The last section discusses the evidence and provides some insights into future research on this topic.

VBP WHERE COST-EFFECTIVENESS IS THE DRIVER

In the United Kingdom, NICE explicitly bases the definition of value on cost-effectiveness and defines explicit WTP thresholds for an additional QALY gained through a new medicine (eg, in England, the threshold recommended for nonexceptional cases is between £20,000 and £30,000 per QALY). The Scottish Medicine Consortium does not apply an explicit WTP threshold even though it uses QALYs as a measure of value. Measuring value through an explicit cost-effectiveness threshold means that the drug requires an assessment of whether the additional health, measured mainly through QALYs, expected to be gained from its use exceeds the health forgone as other NHS treatments are displaced by its additional cost.[13]

Since 1957, the government and industry have set noncontractual agreements to ensure both access to medicines and fair returns for pharmaceutical companies, expressed as levels of sales in the 2014 release of the Pharmaceutical Price Regulation Scheme (PPRS).[14] The PPRS explicitly mentions VBP (since 2014); for example, flexible pricing and patient access schemes can be used for adjusting the price of drugs whose incremental cost-effectiveness ratio is beyond the threshold (patient access schemes) or that exhibit different levels of effectiveness in real life (flexible pricing).

Health technology assessment authorities, and in particular NICE, include the predicted effects of the PPRS in the final appraisal document, thus explicitly linking the cost for the NHS to the incremental cost-effectiveness ratio–based assessment of value. Its explicit and relatively simple mechanism makes VBP in the United Kingdom the most studied example, and its pros and cons have been widely debated. Although reported attributes are mostly homogeneous (simple, explicit, and somewhat predictable method), objections vary and can be categorized into 3 classes. First, concerns about the distribution of benefits between the NHS and industry have been raised. The use of incremental cost-effectiveness ratio thresholds drives prices to levels consistent with the WTP of the demand side, irrespective of the sustainability of such price for the industry.[15,16] Second, adopting the health care and personal social services payer perspective in assessing the incremental cost-effectiveness ratio would lead to underestimating the value of treatment for disease areas in which the benefits affect significantly on non-health care and social costs,[17,18] leading to underpricing.[16] However, the inclusion of other perspectives may bias the focus of assessment, including other dimensions (beyond health) for which the NHS would be required to pay.[19] Third, there is concern about the absence of "size" indicators (eg, prevalence, incidence) in the ICER-based value assessments. If the price is derived as a function of the incremental cost-effectiveness ratio (in the English

case mainly based on QALYs) such that the WTP threshold is met, the size of the target population is not considered (this is a typical feature of cost-effectiveness analysis).[16] The consequence is that the allocative efficiency (ie, maximizing the level of health with the available budget) is pursued only at balanced population sizes, creating imbalances of priorities. Correction mechanisms could be added to include this dimension in decision-making (eg, priority setting, budget impact analysis), but they all act after the price is set.

The inclusion of prevalence and incidence in economic evaluations can insert size considerations directly into the definition of VBP.[20] However, the latest version of the PPRS explicitly states that QALYs are not the only driver of value for the system but that "other factors" should be taken into account. Among these other factors, as of 2017, a budget impact analysis is required for technologies whose estimated impact on NHS value exceeds £20 million.

VBP WHERE COST-EFFECTIVENESS IS NOT THE DRIVER

We illustrate here the available evidence on the application of VBP in those major European countries where cost-effectiveness is not used (or not systematically used) for medicines pricing: France, Germany, and Italy.

In France, the results of the assessment and appraisal processes managed by the Transparency Commission at Haute Autorité de Santé are published on the relevant website (an appraisal document is known as an "Avis"). Economic assessment reports are similarly managed and published on the Economic Evaluation and Public Health Committee (CEESP) website. However, there is no evidence regarding the role played by additional therapeutic value (amélioration du service médical rendu [added therapeutic value] levels 1−3) and cost-effectiveness in price negotiation. Two articles have analyzed the role of cost-effectiveness in France, with a description of the process[21] and an evaluation of the consistency of the reports provided by industry to the CEESP.[12] In the latter, the authors mention that in its assessment, CEESP provides a range of incremental cost-effectiveness ratios at different prices for the assessed drug and that this evidence could be useful for the Health Products Economic Committee, which seems to rely on an incremental cost-effectiveness ratio threshold ranging between €50,000 and €250,000. However, there is no evidence on whether this threshold range is actually used; there is also no evidence regarding the dimension of its impact compared with other domains used in the price negotiation process. Another article[22] investigated the determinants of annual treatment costs (that depend on prices) for orphan drugs. A significant association was observed between the annual treatment cost and the added therapeutic value level, along with the availability of alternative treatment options, the Anatomical Therapeutic Chemical Classification of the indication covered, and the type of comparator used in the pivotal clinical trial.

In Germany, the discounts on list prices (freely determined by industry) are published on the LAUER-Taxe Database. These discounts are negotiated, together with other domains, on the basis of the additional therapeutic value rating. The comparator (appropriate comparative therapy) used to measure the additional therapeutic value is recommended by the Federal Joint Committee (G-BA), and industry may or may not follow this recommendation.

The evidence provided by 2 articles retrieved in the peer-reviewed literature (Table II)[11,23] shows a correlation between the additional therapeutic value and the price premium (net of discounts) over the comparator, whereas the role played by the additional therapeutic value on discounts is less straightforward. More in general, the empirical evidence shows that the negotiation of discounts is unpredictable: regression models that include both value-driven domains (including additional therapeutic value) and budget-driven domains (eg, target-population size) have a low explanatory power of the discount over the list price.

The evidence on Italy is even poorer than that of France, and we were unable to find any evidence on the Spanish model.

In Italy, price and reimbursement negotiation relies in principle on the additional clinical value of the medicine, among other domains (Table I).[9] However, there is no evidence on how the additional value is appraised and whether the price premium is linked with the additional value. It is worth mentioning that since February 2017, while submitting the price and

Table II. Additional value and price setting in Germany (Amnog).

Study	Lauenroth and Stargardt (2017)[23]	Theidel and von der Schulenburg (2016)[11]
Years and drugs covered	2011—June 2016 All drugs, excluding orphan drugs	2011—2015 All drugs, excluding those with no additional value and included in the therapeutic reference pricing system
Methods	Linear regression model	Linear regression model
Dependent variable	Annual treatment cost ratio (new vs comparator)	Discount over list price (%)
Explanatory variables	Additional benefit rating, size of the interested population by additional value	Additional benefit rating, orphan status, comparator (G-BA or Industry driven), data on HRQoL incorporated, population size
Control	Target population, type of comparator (generic vs branded), ATCC	ATCC
Results	+227% price premium if the drug has an additional value (compared with no additional value) +337% with considerable additional value +90% with minor additional value +337% with no quantifiable additional value Larger price-premium with demonstrated effects on mortality	Discount for "no additional benefit": 24.1% Discount for "additional benefit": 20% Additional benefit rating, smaller population size, no deviation from recommended appropriate comparators, and incorporation of HRQoL data are associated with a lower discount, but the model explained only 16.3% of the variations

Amnog = Act on the Reform of the Market for Medical Products; ATCC = Anatomical Therapeutic Chemical Classification; G-BA = Federal Joint Committee; HRQoL = health-related quality of life.

reimbursement dossier, industry may apply for innovativeness status for the relevant drug or indication. Innovativeness status depends on the level of unmet needs and the additional therapeutic value, which is both graded over 5 levels, ranging from "no unmet need/additional value" to "maximum unmet need/additional value"; "moderate" is the minimum level for innovativeness status consideration. The quality of the evidence provided is also considered and graded, and, apart from orphan drugs, a high quality of evidence is required (Figure 2).[24]

Innovativeness appraisals (innovative drug, potentially innovative, or not innovative) are published on the website of the National Medicines Agency (http://www.agenziafarmaco.gov.it/content/elenco-aggiornato-farmaci-innovativi-0), along with the ratings for all 3 domains (therapeutic need, therapeutic added value, and quality of the evidence). Thus far, 38 applications have been appraised: 13 medicines/indications were judged innovative, 13 potentially innovative, and 12 not innovative. Innovative medicines may receive dedicated funding and immediate access, whereas other drugs have been experiencing huge delays due to barriers raised by regional authorities.[25] However, the appraisal document has no formal impact on price negotiation. In fact, in a recently published study,[26] reimbursed prices for innovative

drugs were found to be 32.5% lower than the price proposal submitted by the pharmaceutical company to the National Medicines Agency, compared with 27.4% for all reimbursed drugs, even if innovativeness status was not predictive of the difference between the actual price and the price proposal.

VBP WHERE PRICES ARE NOT REGULATED: THE CASE OF THE UNITED STATES

In the United States, there is no regulation of medicines prices at market launch. By law, drug manufacturers can freely set the price at market launch and negotiate the actual price afterward with insurance companies and other third-party payers, often represented by pharmacy benefit managers. The pharmacy benefit managers are third-party administrators of prescription drug programs for commercial health plans, self-insured employer plans, Medicare Part D plans, the Federal Employees Health Benefits Program, and state government employee plans. In fact, in the United States, there is no single payer but multiple payers with different pricing approaches and WTP different prices for the same drug.[27] Despite the buyers seeking to maximize health benefits for their subscribers at minimum cost, drug prices in the United States are generally 2 to 6 times higher than prices for the same drugs in other major industrialized countries.[28] The public programs Medicare and Medicaid instead benefit from significant price concessions from manufacturers, particularly for drugs that offer clinical advantage or with an alternative mechanism of action.[28,29]

In the last few years, several efforts in the United States have been focused on determining prices for drugs that are commensurate with their value. The Institute for Clinical and Economic Review (ICER-US), an independent organization that assesses VBP, conducted several analyses on drug prices to show the differences between list price and the value-based price. In the United States, a cost-effectiveness ratio of $150,000 or more per QALY gained is not unusual. The ICER-US generally considers technology with a cost-effectiveness ratio below $150,000 per QALY to be of reasonable value, and it creates a "value-based price benchmark" based on prices that fall within thresholds of $100,000 to $150,000 per QALY gained to describe what a fair price might look like for a new technology.[30] For exemple, the ICER-US review of the 2 new proprotein convertase subtilisin/kexin type 9 inhibitor drugs for high cholesterol showed that a reasonable value-based price would be 45%−62% lower than the $14,350 average annual list price. Another ICER-US assessment shows that the fixed combination sacubitril/valsartan for the treatment of heart failure should have a price only 9% lower than the company's list price to align with value for money.[28]

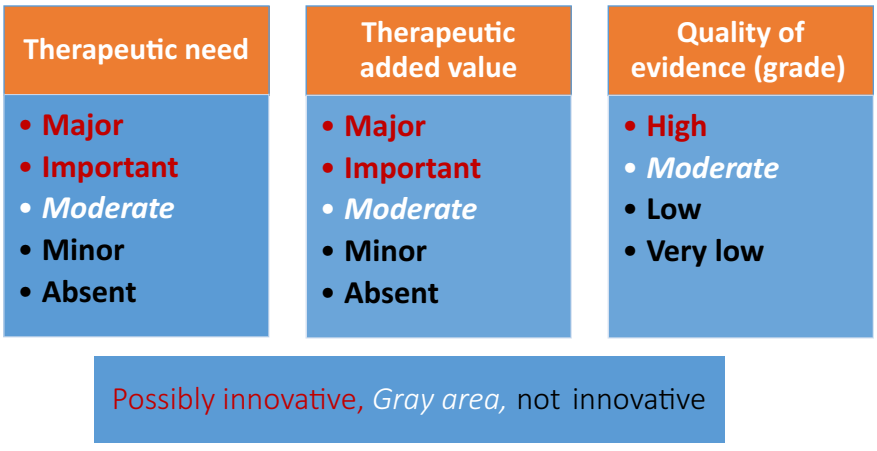

Figure. 2. Domains to determine the innovativeness status for medicines in Italy.

Other actions aimed at applying VBP were recently conducted in the United States. In April 2017, New York State became the first public payer (within the Medicaid program) to authorize limits on prescription drug costs, based on, among other things, their therapeutic benefit. Thus, the state can identify high-cost drugs, determine a value-based price, and use its power enforced by law to negotiate supplemental rebates to achieve this target for its Medicaid program (currently, the basic federal Medicaid statutory rebate for brand-name medications is 23.1% of the average manufacturer price or the average manufacturer price minus the best price available to nongovernmental payers).[31] If spending growth exceeds the 10-year average inflation rate plus 4% in the 2018 to 2019 period, New York's Department of Health is authorized to identify and refer high-cost drugs to a drug utilization review board for a determination of a target rebate amount. The board, in formulating recommendations for VBP, may consider the effectiveness, therapeutic alternatives, and epidemiology of the disease. The same article compared the wholesale acquisition cost versus the actual price charged to New York State to determine the discount attained; this was subsequently compared versus the value-based price range, determined by the ICER-US. For example, the ledipasvir/sofosbuvir wholesale acquisition cost, at May 2017, was $63,000 (8 weeks of treatment) and $94,500 (12 weeks of treatment), whereas the incremental cost-effectiveness ratio value−based price range was $34,000 to $42,000 and the incremental discount required to reach the incremental cost-effectiveness ratio range was 10%−23% (8 weeks of treatment) and 32%−41% (12 weeks treatment).[31]

In the United States, cost-effectiveness analysis to determine drug prices is not usually applied, and VBP is applied in different ways. For example, in December 2017, the US Food and Drug Administration approved voretigene neparvovec-rzyl, a one-shot genetic treatment manufactured by Spark Therapeutics (Philadelphia, Pennsylvania). Because of the high price of this drug ($850,000), the manufacturer promised to reduce the cost through pricing maneuvers that the firm has referred to as value-based. In this way, Spark Therapeutics could offer rebates when patients did not show vision improvement after therapy. The ICER-US assessment on this drug identified a value-based cost at $426,644 (50% lower than list price).[31] The value-based approach based on the incremental cost-effectiveness ratio was adopted by another firm, Regeneron Pharmaceutical (Eastview, New York), which became the first company to publicly use VBP, in line with analysis by ICER-US, for dupilumab.[32]

As previously mentioned, in contrast to other countries, the United States allows market forces to determine prices. Comanor et al[29] examined medicines pricing in England and the United States, concluding that VBP is enforced by both regulatory and market processes, with similar outcomes. The study compared launch prices for new drugs and the price of the standard of care in both countries, measuring the price increments that newly introduced drugs had over the older drugs they replaced. Their results suggest that there is no indication that the British regulatory structure leads to different relative prices from those found in the United States. They thus affirmed that VBP is present in both countries without evidence that regulation leads to outcomes different from market mechanisms.

DISCUSSION

This article reviews the evidence on whether and how VBP is actually implemented in several European countries and the United States. Based on the operational VBP framework suggested by the literature[5] and the main findings of our analysis, two possible application models emerge: (1) direct models in which cost-effectiveness is a driver; and (2) indirect, multi-attribute models, characterized by greater discretion on the integration between the different domains and the evaluation of coherence between cost and value. The direct model is illustrated by the United Kingdom, where the value of a drug is explicitly based on cost-effectiveness thresholds for additional QALYs. In indirect, multi-attribute models, cost-effectiveness is not a driver (as in the case of France, Germany, and Italy), and it is harder to identify evidence of actual implementation of VBP unless there is a clear, predefined link between added value and the premium price as well as transparency in the way added value is measured and converted into a premium price (or a lower discount). In general, for countries relying on indirect, multi-attribute models, it is difficult to

determine whether pricing is mostly driven by value (value-for-money) or impact on budget (sustainability). The United States represents another example of the indirect, multi-attribute model, in which prices are not regulated and VBP is applied differently.

Several additional considerations can be drawn from VBP in the United Kingdom, as the most explicit and widely applied of the models discussed. First, one of the main concerns in VBP applications is how the benefit surplus generated by the drug might be unevenly distributed between the payers and the producers, with great variation from case to case. As a result, companies may experience very high or very low returns on research and development costs, making their business case much more volatile. Second, VBP is defined on a single patient basis and is independent of volume, meaning that a VBP approach cannot take the size of the target population into consideration. Supporters of VBP would consider budget impact as a second-order driver, but budget constraints may actually be the most important determinant of price negotiation.

Despite vastly different regulations governing price negotiation and the formal adoption of VBP in various countries, a review of the evidence on the actual implementation of VBP has been lacking in the literature. The present article addresses this need but also shows how the evidence is still limited. Future empirical research should take the opportunity to bridge this gap, especially in European countries such as France, Spain, and Italy.

DISCLOSURES

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