

# PRICING MEDICINES: THEORY AND PRACTICE, CHALLENGES AND OPPORTUNITIES

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**Abstract** | The pricing of medicines has become one of the most hotly debated topics of recent times, with the pharmaceutical industry seemingly being attacked from all quarters. From a company perspective, determining the price for each new product is more crucial than ever, given the present dearth of new drug introductions. But how are pricing strategies developed in practice? What is value-based pricing and how are financial models of return on investment constructed? What are the challenges faced in setting the price for a particular product, and how will scientific and environmental trends provide future pricing challenges or opportunities?

## A GUIDE TO DRUG DISCOVERY

**NEW MOLECULAR ENTITY**  
A medication containing an active ingredient that has not been previously approved for marketing in any form.

“There is no other country on earth that allows the pharmaceutical industry to leverage these extraordinary extortionate prices for lifesaving drugs out of their citizens.”<sup>1</sup>

As exemplified by the above statement made in the United States House of Representatives on 6 May 2004, the prices of pharmaceutical products are being constantly criticised in the United States, and they are also subject to increasing challenges throughout the rest of the world. There is growing support in the United States for the legal importation of drugs from Canada and other countries in which prices are typically lower. These lower prices generally result from strict controls, which not only constrain the price of new drugs at launch, but also prevent increases over time; both of these factors contribute to the widening price gap between the United States and the rest of the world. As the United States begins to provide federal funding for outpatient drugs for individuals in the Medicare programme, the scrutiny of drug prices and the negotiations to reduce them are likely to intensify.

Although the public perception of the pharmaceutical industry might be of unscrupulous ‘price gougers’, certain fundamental aspects of drug development and the markets in which drugs are sold have an important

bearing on the prices that are charged by the industry. First, drug development is risky, with high costs that must be incurred years before any returns can be realized. Second, although they are patent protected, most branded products are in fierce competition for market share with other products that provide similar benefits, as is the case in other industries. Third, for breakthrough products that have no obvious competition, the price charged must generally be supported by their economic, as well as their clinical, value or the product will not be purchased.

The present focus on drug prices is related to funding pressures and ‘affordability’. With the ageing population and the continual development of new medical technologies — which only increase the number of people who live higher-quality and longer lives — a fundamental question for societies becomes: ‘What proportion of our national income are we prepared to spend on improving the length and quality of our lives?’<sup>2</sup>

Although an individual pharmaceutical company might be unable to address these broader social questions, the slow-down in the introduction of **NEW MOLECULAR ENTITIES** (NMEs) during recent years, as well as the increasing downward pressures on prices, has heightened the importance to companies of maximizing the

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return from those NMEs that are launched. This, in turn, has increased the emphasis on setting an economically viable launch price, which normally also means a price that will ensure adequate reimbursement. The importance of the launch price is underscored by the fact that price controls in much of the world preclude any subsequent increases in price after launch.

The process of determining the price for a new product starts early in development, several years before launch. The pharmaceutical company must estimate the value of the product to its customers as well as the willingness and ability of different consumers to pay for it. The company must also determine a price threshold above which the return on investment (ROI) in research and development will be sufficient to satisfy its investors.

In this article, we describe the methodological framework that is used by many manufacturers to set the price of new drugs, highlighting the challenges that are encountered and the complex trade-offs that must be managed, as well as outlining how emerging trends could influence the practice of pricing and value justification in the future.

### Pricing basics

Although the details can seem formidably complex, the basic principles that underlie the pricing of a pharmaceutical product are similar to those for most other products or services. Essentially, the limits on a viable pricing range are determined by assessing the product from two different perspectives: the market perspective and the company perspective. The market perspective consists principally of an assessment of the value of the product to its customers in the context of the competitive environment. This market or 'value-based' perspective on price is the primary focus of pricing-strategy development and tends to establish the upper limit on a viable price range. An internal company assessment of costs and ROI requirements must accompany the market perspective setting. A price above the ROI thresholds of the company is equally important as setting a price at, or below, the maximum that the market will bear; therefore, the ROI considerations of a company tend to fix the lower limit on viable price. The relationship between the market perspective, the company perspective and the viable price range is illustrated in FIG. 1.

In contrast to historic pricing approaches for which the company perspective was dominant and product prices tended to be set on a 'cost plus margin' basis, pricing theory and practice now recognize that the needs and perspectives of the customers must be the starting point for pricing-strategy development. This applies as much to pharmaceutical companies as to any other industry. In essence, the fundamental pricing question has shifted from 'What price do we need to charge to cover our costs and make a good return?' to 'Given market perceptions of value, which products can we profitably produce?'

### Market perspective and value-based pricing

Value-based pricing is a broadly applicable conceptual framework for assessing the value of a product (or

service) to a customer in the context of alternative offerings, and setting a price relative to that value. It underlies most modern pricing theory and is explained by the following simple formula:  $V = R \pm D$ . Here, the perceived value ( $V$ ) of a product to a specific customer is equal to the reference price ( $R$ ) — which is the price of the best alternative or reference product — plus the net value of the perceived differentiation ( $D$ ), which can include a mixture of both positive and negative characteristics that are offered by the new product. This formula is illustrated in FIG. 2. The concept of net differentiation recognizes that not all of the differentiating characteristics of a new product will necessarily be positive. For example, in the pharmaceutical context, a new drug with improved efficacy might also have a less convenient dosing regimen or an inferior safety profile. Products that offer a net positive differential value, as shown in FIG. 2, will have a perceived value that is higher than the reference price, and therefore there is an opportunity to set their price at a premium to the reference product. Conversely, products that are deemed to have a net negative differential value will need to be priced at a discount to the reference product to attract purchasers.

The appeal of this simple framework is that it intuitively fits with how we, as consumers and 'purchase decision-makers', evaluate price as part of purchase decisions, whether consciously or subconsciously. 'Is product or service X worth the extra money?' is a common and recurring question that is asked during purchasing decisions throughout daily life.

One important implication of the value-based approach is that pricing strategy involves more than just setting a price. Strategic pricing should be seen as 'capturing the value' that is generated in the product, which, in turn, highlights the crucial importance of understanding early in development what constitutes 'value' and of subsequently using customer value considerations to guide product-development decisions. In this way, the role of a pricing strategy shifts from simply reactive 'price setting' at product launch to proactive influencing of value generation throughout development, with a view to ultimately capturing that value.

To demonstrate some of the issues and challenges of successfully applying value-based pricing to pharmaceuticals, including the implications for product-development decisions, we must examine each of the components of the construct.

### The product

The question of defining the product during pharmaceutical development is not simple. Development generally starts with a molecule that might have potential uses in several, often very different, indications. With each indication, the intended place in the treatment regimen (for example, line of therapy, target patient segments, treatment setting, mode of administration and so on) further delineates what the product will be, with resultant implications for identifying the relevant customers and competitors, and, therefore, the differential value and pricing opportunity.

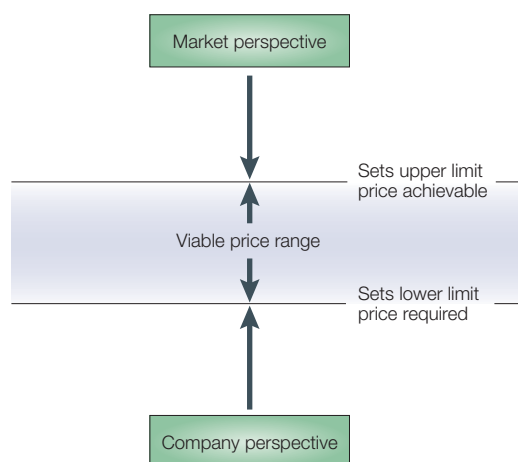


Figure 1 | **The balance between the market and company perspectives determines the viable price range.** A product price needs to fall between the maximum the market will bear and the minimum the company can accept and still make an adequate return.

As an illustration of the importance of positioning on price, the recent recommendation by the National Institute for Clinical Excellence (NICE) in the United Kingdom to endorse tacrolimus (Prograf; Fujisawa), but not pimecrolimus (Elidel; Novartis), for the treatment of **atopic eczema** was based, in part, on the intended positioning of each drug in the treatment regimen. Pimecrolimus is licensed for first-line use in patients with mild-to-moderate disease, in whom its benefit over the reference product of topical corticosteroids was not considered to provide good value for money. By contrast, tacrolimus is approved for second-line treatment of moderate-to-severe disease, a positioning in which its incremental value versus the continual use of high-dose corticosteroids was deemed worth the price (note that following an appeal by Novartis, pimecromilus was subsequently recommended for use in the same patient groups as tacrolimus).

To avoid surprises when the drug reaches the market, it is crucial to recognize at an early stage how different development strategies will result in very different products from the perspective of value and price. To this end, the construction of a series of well-defined product scenarios, considering the price/value implications of alternative placements in the treatment regimen and different target patient populations, is an essential input to early development.

A particular challenge for development strategy is the choice and sequencing of indications. Different indications generally involve distinct customers, value propositions and competing (reference) products, as well as different doses. Examples of molecules that treat multiple indications include finasteride (Propecia; Merck) for **benign prostatic hyperplasia** (BPH) and alopecia (hair loss), and anti-convulsants such as gabapentin (Neurontin; Pfizer for both epilepsy and neuropathic pain). Although the value-based approach might theoretically justify appreciably different prices in each indication, in reality it is not viable to achieve

large price spreads in a given country for the same molecule on the basis of differing indications, unless a differing dose relationship supports this. Early evaluation of cross-indication pricing opportunities, risks and trade-offs is therefore an important factor guiding indication sequencing and development strategies. Resulting strategies could include the following: developing and launching higher-priced indications ahead of lower-priced ones, thereby securing a higher-priced 'anchor point' for subsequent indications; targeting the product in the lower-priced indication towards a higher-priced patient subpopulation (this would probably be a severe, and therefore typically smaller and more needy, patient subpopulation, for whom the value of the product might be more commensurate with a price that is in line with the initial higher-priced indication); and developing different formulations (for example, tablets versus injections) for different indications to enhance the possibility of separate pricing to capture the value of each indication.

### Reference price

As discussed above, the reference product and therefore the reference price for a new product depend primarily on its intended indication and place in the treatment regimen. The reference product is generally the present standard of care, but challenges (or opportunities) arise in several situations. First, if there is no contemporary drug therapy for the condition; this can serve as an opportunity to, for example, reference a new drug therapy to an existing expensive surgical procedure, as cimetidine (Tagamet; GlaxoSmithKline), which was the first histamine H<sub>2</sub>-receptor antagonist, was able to do against stomach surgery in the case of ulcers in patients with high levels of gastric acid. Second, if there has been no pharmaceutical innovation in the disease area for some time and the present standard of care is old, generic or cheap; this increases the burden on the manufacturer to robustly demonstrate and communicate a substantial positive differential value to secure pricing commensurate with an innovative product. This was the case for the atypical antipsychotics that are used against **schizophrenia**; they achieved a price level that was notably higher than that of typical antipsychotics because they had fewer side effects, and the effect of this on patient compliance, leading to lower levels of hospitalization and, therefore, reduced healthcare costs, was successfully demonstrated. Third, if the standard of care differs depending on the country or region in question; this can lead to difficult trade-off decisions when crafting a global strategy. Fourth, if the future standard of care, which will probably become the reference product, is still in development by another company and the pricing is not yet known.

As the reference forms the basis for the value perception of a new product by the buyer, a crucial part of pricing-strategy development is framing the value of the new product in the comparative context of the desired price reference. Equally important is steering the customer away from comparisons with undesired price references.

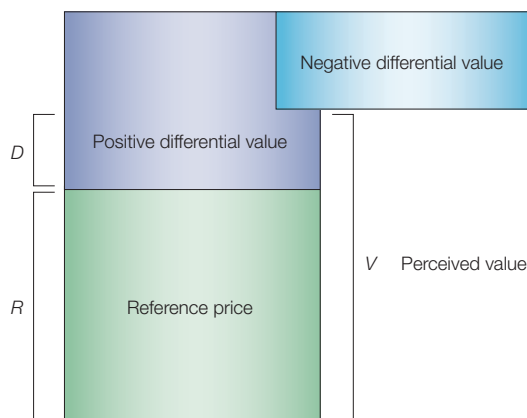


Figure 2 | **The components of perceived value.** The perceived value ( $V$ ) of a product or service is equal to the price of the reference product ( $R$ ) plus the net value of the perceived differentiation ( $D$ ). Based on concepts described in REF. 11.

Undesired price references are particularly relevant given the increasing use of therapeutic price-referencing systems by health authorities as a means of controlling drug costs. Under many of these systems, principally in Europe, products are grouped into common therapeutic categories using the ‘ANATOMICAL THERAPEUTIC CHEMICAL’ (ATC) CLASSIFICATION SYSTEM<sup>3</sup>. The reimbursed price of a product falling into a particular category might be restricted to the average, or even the lowest, price in that category. Any difference between the reimbursed price and the actual price that is charged must be borne by the patient, which normally has the effect of forcing the manufacturer to adjust its price to the reimbursed level. By using such therapeutic referencing systems, payers inherently ignore any value differences between drugs in the same ATC class and, consequently, impose a single price on the entire class. Manufacturers of new innovative products will clearly seek to demonstrate a value difference from existing drugs to avoid being grouped with older cheaper drugs, which could severely limit the price potential of the new product. One way of framing the new product as separate from an existing class or category is to apply for a new ATC code early in development, as long as sufficient evidence can be provided to back this new categorization.

Another common challenge in price-reference framing is convincing the buyer of a particular price reference when no head-to-head clinical studies have compared the new drug to the reference product. In some cases, buyers will accept indirect comparative analyses, such as meta-analysis, although a clinical comparative study is generally far more compelling. The choice of clinical trial comparator therefore needs to be made in full awareness of the potential influence on pricing and reimbursement, as well as the more traditional considerations of technical risk, costs and ‘speed to market’.

In cases in which the present gold standard is an old generic therapy, which could set an unfeasibly low price reference for the new product, it might be appropriate to introduce an indirect reference product into the price negotiation and communication process, for comparative

purposes. This indirect reference is often a newer higher-priced product in a related therapy area, with a perceived relative degree of innovation that is similar to the new product in question.

### Differential value

The introduction of added value to present medical practice is generally the reason for developing new pharmaceuticals. Differential value over existing therapy (or filling an unmet medical need) clearly varies by disease area, but generally consists of a mixture of clinical, economic and quality-of-life improvements. The differential value of a new product also varies greatly depending on its place in the treatment regimen and between patient segments.

To be successfully incorporated into a value-based pricing strategy, the differential value for the new product must be identified, demonstrated, quantified and communicated.

**Demonstrating value.** Not surprisingly, the primary means of demonstrating the differential value of a new pharmaceutical is through the clinical trials programme and, particularly, through Phase III pivotal trials. The choice of endpoints, patient populations and the overall design of these trials are crucial factors in influencing the perceived value of the new product to the relevant customers. With the payer taking on an increasingly important role as the audience for the value proposition (as discussed further below), pharmaceutical companies need to ensure that the value drivers of a new product from a payer perspective are clearly identified and considered as part of the Phase III design process. If reimbursement at a premium price is ultimately sought for the product in certain patient populations on the basis of specific value claims, the company will want to ensure that those patients are included in sufficient numbers, and that the relevant endpoints are measured, in the Phase III programme.

**Quantifying value.** The issue of how to quantify the differential value into a number for pricing purposes can be difficult and generally requires qualitative judgments in addition to robust analysis. The net differential value provided by a new product can be made up of differences from the reference product in several product attributes, although it is normally anchored principally around an improvement in either an efficacy or a safety parameter. Small-to-moderate improvements in therapeutic value might, in some markets, be captured in price — in the form of a small premium — without the need for extensive quantification of the economic value of that differentiation. However, the larger the expected differential value of the new product (that is, the greater the therapeutic advance and, therefore, the price-premium potential) the greater the need to quantify and support the economic value of that differentiation.

A common way to ‘home in’ on a reasonable value quantification and, therefore, price is to ‘triangulate’ using a range of approaches. Although different price options will generally be tested with end customers for

<sup>3</sup>ANATOMICAL THERAPEUTIC CHEMICAL’ (ATC) CLASSIFICATION SYSTEM  
This was set up by the World Health Organization (WHO) as a tool for research into drug use, and divides drugs into different groups according to the organ or system on which they act, and their chemical, pharmacological and therapeutic properties.

acceptance using pricing research, there are two important points of reference for initial attempts to quantify the differential value of a new therapy: first, empirical evidence of the market acceptance of differential prices for different outcomes, based on analogues of existing marketed therapies; and second, normative measures, such as pharmacoeconomic metrics.

The relevance of an analogue depends on the similarity of the subject product and market to the new therapy in question. Looking at products in the same therapeutic area generally gives a more reliable indicator of the willingness to pay for incremental benefits of the new product; however, this might not be possible if there have been no significant innovations in the therapy area for some time or if it is an uncharted area for a pharmaceutical. In some cases, it is possible to define the therapy area relatively broadly and still gain useful insight. For example, drugs that are used to treat cardiovascular disease are generally viewed as having a common ultimate aim: to reduce the risk of major adverse cardiovascular events. The 'price per incremental percentage risk reduction' of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), is regarded informally by some payers as a benchmark for quantifying the differential value of new cardiovascular agents.

The growing discipline of pharmacoeconomics is becoming increasingly important in providing the methodological framework for quantifying the economic value of a new product compared with present therapies. Pharmacoeconomics, when properly applied, incorporates value-based pricing into its analytical approach and provides a reference point for quantifying the differential value of a new pharmaceutical.

The pharmacoeconomic value of a new pharmaceutical product is generally measured by a comparison of the change in total health care and other costs with the change in health outcomes that are associated with the use of the new product<sup>4,5</sup>. Changes in costs include the acquisition and administration costs for the new product compared with those for the drugs that the new therapy might replace, as well as changes in the costs that are associated with treatment of the disease and with side effects. Also included might be changes in productivity-related costs and other indirect costs. For a drug-value analysis, changes in health outcomes are most commonly measured in changes of quality-adjusted life years (QALYs), which are computed on the basis of the level of well-being in alternative health states and the duration of time in each alternative health state, both with and without the new drug. The ratio of changes in costs divided by changes in QALYs is computed to calculate a cost per QALY for the new drug. Many countries now incorporate a review of pharmacoeconomic evidence as part of their assessment of whether to recommend reimbursement or usage of a new product at the price that is requested by the manufacturer. In the United Kingdom, for example, NICE uses a threshold of £30,000 per QALY to set the upper limit on willingness to pay for therapeutic advances. By conducting

the relevant analyses, manufacturers can use such metrics to estimate a price at which a new therapy falls within the accepted range.

An important challenge in demonstrating and capturing value for chronic therapies is the fact that the differential value of a new product is often based on its projected influence on long-term health outcomes. Clinical trial data that are submitted for product registration, however, might only provide evidence of the effects on surrogate endpoints from short-term studies. Payers commonly seek to delay reimbursement or refuse premium pricing until the results of studies of long-term outcomes are complete. Manufacturers often use economic models, which are generally received with scepticism by payers, to attempt to demonstrate the link between the surrogate results that are shown in clinical trials and the projected long-term outcomes from the drug. Given that, in most countries, it is not possible to raise prices once they are set, the conundrum for pharmaceutical companies is managing the trade-off between launching earlier at a lower price versus launching later (after the results of studies of the long-term outcomes have become available) at a higher price. In practice, most companies have historically chosen the former option; however, innovative strategies, such as risk-sharing approaches, are increasingly being considered to overcome this hurdle. A risk-sharing strategy can be applied if there is partial evidence that a new product has significant value, although it might require long-term or 'naturalistic' studies to robustly confirm this. Under these circumstances, the pricing authority might allow the launch of the product at a premium price on the condition that these naturalistic studies are performed. The drug price might then be amended once the outcomes are known. In this way, the manufacturer has assumed part of the risk that the product will not work in the real world as projected on the basis of the clinical trial data. Examples of the application of risk-sharing strategies have involved treatments for **multiple sclerosis** in the United Kingdom and **Alzheimer's disease** in Italy. In both countries, the authorities are paying for drug treatments only if they have proved effective in the patients to whom they were administered, as demonstrated through modified forms of naturalistic clinical studies.

**Communicating value.** The traditional pharmaceutical marketing communication channels, such as the sales force, journal advertising and scientific publications, all have a role in communicating the value of a new product to its customers. However, these traditional channels tend to focus on either top-line product messages, or specific aspects of the product or disease profile. Increasingly, the vehicle that is used for communicating the most complete picture of the differential value of a product is a 'value dossier', which is aimed specifically at the payer, and focuses on the clinical and economic differentiation of the product in the context of the contemporary treatment environment. It is also becoming common to see the establishment of a more comprehensive value-communication strategy that is focused

Purchase decision maker	Form of purchase decision	Purchase decision criteria include:
Payer/gatekeeper	"Should I reimburse this product/add product to formulary?"	<ul style="list-style-type: none"> <li>Disease priority/unmet need</li> <li>Clinical innovation</li> <li>Budget impact</li> <li>Quality of evidence</li> <li>Health economics</li> <li>Political motives</li> <li>Level of physician demand</li> <li>Level of patient demand/advocacy</li> </ul>
Prescriber	"Should I prescribe this product?"	<ul style="list-style-type: none"> <li>Expected clinical improvement</li> <li>Patient financial impact</li> <li>Personal financial impact</li> </ul>
Patient	"Should I accept this prescription/fill this prescription?"	<ul style="list-style-type: none"> <li>Prescriber recommendation</li> <li>Co-pays/out of pocket</li> <li>Quality-of-life impact</li> </ul>

Figure 3 | **Pharmaceutical purchase decision-making.** The payer, prescriber and patient can each play a role in the purchase decision for a pharmaceutical.

on the payer, which begins at Phase III or sooner. This is particularly important for products that are expected to have a large effect on the drug budget, and/or if the current burden of the disease is not well understood and needs to be highlighted.

**The customer**

In most industry- or consumer-purchase situations, the same person or entity initiates the purchase of a product, uses it and pays for it. The target audience for the manufacturer, for the purposes of valuing and pricing a product, is therefore clear. With medicines, however, these three roles are normally segregated and are filled by the prescriber, the patient and the payer, respectively. To some degree, each of these three parties has an influence over the purchase decision for a particular product, in which price will probably have a role. The form of the purchase decision and the sample criteria that are used for making that decision differ for each party, as depicted in FIG. 3.

In addition to having different value perceptions and, therefore, different purchase-decision criteria, each of these stakeholders is influenced to some extent by the perceptions and actions of the others. For example, a payer might be strongly influenced in the decision to reimburse a product by pressure from physician and/or patient organizations. Similarly, the decision of a doctor to prescribe might be affected by the reimbursement/formulary status of a drug. So, understanding the price/value trade-off — and the effects on the purchase decision — for each of these three parties, as well as the interactions between them, is crucial to estimating the overall ‘system’ reaction to a particular pricing strategy.

The importance of each party as a target audience for pricing-strategy development varies depending on the country and the product in question (BOX 1). For example, prescribers in health-care systems that are subject to some degree of budget responsibility (such as in Germany or the United Kingdom) are generally more price sensitive than those operating in systems in which the drug-budget ‘gatekeeper’ role is elsewhere (such as in France, where the gatekeeper is at a national level and prescribers are generally insensitive to price). In addition, for products in which a large proportion of the price is an out-of-pocket cost to a patient — for example, ‘lifestyle’ products such as erectile-dysfunction drugs — the price sensitivity of patients is heightened and the patient perspective needs to be carefully considered in the pricing strategy. As illustrated by these two examples, the importance of a particular stakeholder for value estimation and pricing strategies tends to be proportional to their role in paying for the product.

Therefore, the formal payer or financial gatekeeper (whether national or local, public or private sector) has increasingly become the primary focus of value generation and pricing strategies for pharmaceuticals. In many markets around the world, the payer is a monopsonistic (single) buyer who imposes strict regulations as to how ‘therapeutic added value’ is measured and rewarded in price. Understanding how payers will value therapeutic advances, and what evidence they require to demonstrate those advances, is a crucial component of value estimation and price planning. As stated previously, these issues must be considered by pharmaceutical companies early in development and certainly before the design of the pivotal studies programme is finalized.

In addition to assessing the value for money of a new therapy, the issue of affordability is an increasingly prominent focus of payers who are faced with rapidly escalating health-care expenditure. The prevailing ‘silo mentality’ in many parts of the world, in which drug budgets are generally seen as fixed and separate from other health-care budgets, presents a continual challenge to pharmaceutical companies, whose new drugs will often add to that drug budget<sup>6</sup>. Even in situations in which robust evidence indicates that a drug will lead to reductions in costly events elsewhere in the health-care system — and, therefore, satisfies the ‘value-for-money’ test — in many countries, the drug-budget barrier serves as a drag on the sales uptake of new therapies during the early post-launch years. Owing to fears of exploding budgets, payers often seek to either negotiate down the price that is sought by the manufacturer, or allow the price but with highly restricted usage criteria. Manufacturers should anticipate situations in which budget effects are likely to be a concern and ensure that options, such as segmented patient strategies, are available for use in price negotiations.

**The company perspective**

Although the value perceptions of the market form the initial focus of pricing-strategy development, from the perspective of the company it is also crucial to ensure that the value-based price, with the resultant

**Box 1 | The influence of different health-care systems on pricing**

Differences in the structure of health-care funding between the United States and Europe result in different pricing environments. The United States is unique in its health-care model, in which most patients are covered by private, mainly employer-funded, insurance schemes, some patients are eligible for government health programmes and a substantial minority of patients is left with essentially no coverage. The numerous private insurers offer varying benefit packages with alternative levels of pharmaceutical coverage. People choose the level of coverage that they desire, although their choice might be restricted by affordability and the plans that are available through specific employers. In Europe, national health systems dominate and provide health care to all, with funding through a mixture of taxation and national insurance systems. Health care is generally free at the point of delivery and is based on the principle of need, rather than the ability to pay.

The US financing model has led to a free market for drug pricing, with prices subject to market forces, such as competition and customer negotiating power. Product launch is possible immediately post-approval for most products and drug prices are negotiated with insurers to secure access on formularies. Prices for products that are reimbursed under government health programmes are generally based on the market price of the drug, but are often subject to mandatory discounts. Patients without insurance coverage must typically pay almost the full list price for medicines.

In Europe, the insurer is often effectively the sole buyer for each country, which creates a 'monopsony'. In France, for example, each new product is reviewed by national authorities that compare the product to present alternatives, classify the drug on a scale ranging from a 'major therapeutic advance' to 'no therapeutic progress', and propose a price based largely on this assessment. In this situation, the purchaser clearly has immense negotiating power. Drug prices in Europe are further constrained by cross-national price referencing and parallel trade between countries.

Despite the differences, there are many similarities between the United States and Europe. These include the following: formularies in the United States are comparable to positive lists in Europe; tiered co-pays in the United States are analogous to the tiered levels of reimbursement in Europe; buyers in the United States often demand supplemental rebates whereas European governments can impose mandatory price cuts; and the United States is considering legalizing re-importation whereas Europe allows parallel trade.

Also, although pricing flexibility is presently greater in the United States, the recent passage of the Medicare drug benefit, with the consequently increased drug-funding role of the US government, might cause the environment in the United States to become even more similar to that of Europe.

implications for revenue and profit, will ultimately lead to the product generating an adequate ROI over its development and marketing lifecycle.

When criticizing pharmaceutical company pricing policies, the popular press frequently focuses on the high gross margin of drugs — the difference between the unit price and the unit production cost. For the pharmaceutical company, however, a high gross margin is needed if the product's NET PRESENT VALUE (NPV) is to be positive. This is because there might be 10 or more years of research and development costs, without any revenue generation, before the product begins to generate gross margins. Therefore, the gross margin needs to cover these research and development costs, as well as the continuing production and marketing costs. A hypothetical cash-flow curve for a pharmaceutical product is shown in FIG. 4. The shape of the uptake curve, which starts shortly after the product launch, is usually highly sensitive to product price, as is the revenue per unit sold.

In an NPV calculation, a discount rate is chosen that represents the opportunity cost of capital, which is defined as the financial return that could be obtained by

investing capital in the next-best alternative investment. A discount rate of 10–12% is generally chosen in the pharmaceutical industry as the standard rate at which to value most of the products or programmes that are in development; a higher rate might sometimes be applied to reflect products that are considered to be particularly risky.

The NPV of discounted revenue minus discounted costs is computed over the full product development and marketing lifecycle. Many types of cost must be incorporated into the NPV calculation, along with their timing during drug development. These include the following: preclinical costs, clinical development costs, stability testing and manufacturing scale-up costs, the costs of goods produced and marketing costs. These must be combined in the NPV calculation with estimates of the price and volume of future sales. Both costs and revenues in the NPV calculation are adjusted based on the probability of the drug proceeding through each phase of development. In general, for every 5,000 molecules that are tested in the laboratory, only 5 reach Phase I and only 1 will actually be marketed<sup>7</sup>.

A threshold minimum product price can be computed as the price for which the NPV calculation yields a positive value or is greater than a target value. If this price is lower than the maximum feasible price from the market perspective, then the investment should be considered viable.

The NPV is calculated and updated continually along the product development timeline as new clinical and market data become available. The calculation is especially important before crucial cost-investment decisions, such as the initiation of Phase I trials, the initiation of Phase III trials and investment in manufacturing capacity. The need to make these investment decisions early — often many years before launch — underscores the importance of developing and testing the price assumptions in the NPV calculation at a similar early stage in development.

**Global price interdependency**

Although the importance of customer value estimation and company ROI are common to all industries, the issue of price interdependency between different countries is a particularly acute challenge for pharmaceutical companies. The phenomenon of the price in one country influencing the prices in other countries is enacted principally through two processes: cross-border price referencing and parallel trade.

Cross-border, or geographic, price referencing is a price-control mechanism whereby the health authority in one country references prices in a select group of other countries when determining the maximum price that it will pay for a drug. In some markets, such as The Netherlands, the health authority references the average price; in others, such as Greece, the lowest price is referenced. Although many countries use price referencing only at launch, others, such as Spain, also operate retrospective systems whereby the launch price is subject to ongoing downward adjustment based on any post-launch price movements in the referenced countries. Geographic reference pricing has a direct

NET PRESENT VALUE (NPV). The difference between the discounted projected revenues and the discounted projected costs over the product lifecycle.

Table 1 | **Disease and product drivers of price sensitivity**

Disease or product characteristics	Degree of price sensitivity	
	Higher sensitivity (lower prices)	Lower sensitivity (higher prices)
<b>Disease/patient characteristics</b>		
Chronic/acute	Chronic	Acute
Prevalence	High	Low
Perceived disease severity	Low	High
Unmet need	Low	High
Asymptomatic/symptomatic	Asymptomatic	Symptomatic
Patient severity	Mild	Severe
Patient age	Old	Young
<b>Product characteristics</b>		
Product influence on unmet need	Low	High
Mode of administration	Oral	IV/parenteral
Formulation	Chemical	Biological
Offsetting cost savings	Low	High
Effect on patient's life	Enhancing	Extending
Differentiation from competitors	Small and unclear	Clear and large

New-product pricing: although there are exceptions, the table illustrates the typical relationship between certain disease or product characteristics and the degree of price sensitivity in the market, with lower price sensitivity implying receptivity to higher price levels. IV, intravenous.

influence on prices worldwide. Initiated in Europe, it is now global in scope, with countries as geographically diverse as Japan, Canada, Brazil, Korea and Taiwan all operating such systems.

Parallel trade is a less direct way in which prices from one country have an influence on those in another. This occurs when a wholesaler buys a product in a low-priced country and imports it into a higher-priced country, thereby undercutting the local price in the importing country. This arbitrage has occurred in Europe since the 1970s and is explicitly encouraged by Article 81 of the European Union Treaty of Rome for the free movement of goods. The trade sometimes reaches such high levels that the local affiliate in the high-price country feels compelled to reduce prices to compete with the imported products. Although first seen in Europe, parallel trade is spreading to many other parts of the world and will be seen in the United States if proposed legislation legalizing the importation of drugs from Canada is successful. Unlike price referencing, in which the cost savings from lower prices directly benefit the health-care system that is conducting the referencing (albeit at the expense of the manufacturer), there is evidence that the main beneficiary of parallel trade is often the arbitrageur, or middleman, with relatively little of the cost savings passed on to the health authorities or end consumers<sup>8,9</sup>.

In light of this increasing price interdependency, manufacturers need to maintain a global perspective when planning pricing strategies and making price decisions. Although it is still necessary to initially determine the optimal price for each country individually, an understanding of how those prices interact globally is an important prerequisite to developing a global pricing strategy.

### Setting the launch price

**Country prices.** Assuming appropriate preparatory work has been conducted throughout the development process, in terms of estimating price potential and concurrently optimizing product development to maximize the pricing/commercial opportunity, development of the final launch price for a new product generally occurs between registration and technical approval.

For countries without formal price controls (such as the United States, the United Kingdom and Germany), a manufacturer is free to launch at its desired price immediately after attaining marketing approval. Before this, the company normally conducts price-sensitivity testing with physicians, patients and/or payers (depending on the product) to validate the planning price estimates and set a profit-maximizing price.

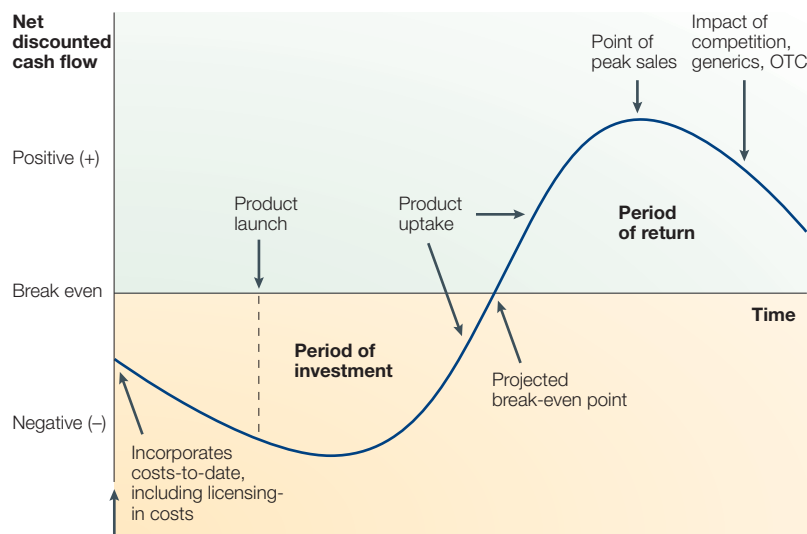
For price-controlled markets, such as France, Spain and Italy, if reimbursement is sought then price negotiations with government authorities are required to set an agreed price at which the product can be launched. For the manufacturer, the pre-launch phase for these countries involves preparing for the negotiations, including estimating the price threshold and likely volume constraints of the payer, and developing opening and fallback negotiating positions. A crucial input to this planning and the subsequent negotiations will be the final label that is received at regulatory approval.

For both 'free-price' and price-controlled markets, the probable actions or reactions of competitors can be an important consideration. With many manufacturers pursuing common disease targets and often developing products in the same class, close races to reach the market frequently result. Examples include the 'glitazones', rosiglitazone (Avandia; GlaxoSmithKline) and pioglitazone (Actos; Eli Lilly), for **type II diabetes**, and the cyclooxygenase 2 (COX2) inhibitors, celecoxib (Celebrex; Pfizer) and rofecoxib (Vioxx; Merck), for arthritic pain. In these situations, understanding the effect of the pricing strategy of a competitor on the pricing strategy of the company — and vice versa — is crucial, and can have an important effect on the level of commercial success that is attained.

**Global optimization.** Given the interdependency between prices across countries, the finalization of individual country prices without considering the global effect is unwise. To ensure that prices in certain countries do not inadvertently result in negative effects elsewhere in the world, many global manufacturers conduct global pricing optimization exercises, which take into account individual optimal country prices, price-referencing mechanisms and probable parallel trade patterns, to determine a set of prices (and, usually, a price corridor or price floor) that are optimal for the company at the global level.

### Future trends and implications

Driven by ageing populations and fuelled by the introduction of expensive new technologies, the imbalance between the demand for medicines and the ability to fund them has led to acute cost pressure in most developed nations. Depending on the country, the response



Proof of concept/Phase II

**Figure 4 | A hypothetical cash-flow curve for a pharmaceutical product.** A long initial period of negative cash flow is typical; a high gross margin is required to recoup, and provide a return on, this investment. OTC, over the counter.

to this pressure has generally been to focus on some form of either cost shifting, cost containment or drive for health-care efficiency, which variously serve as challenges or opportunities for the pharmaceutical industry.

In most countries that are covered by social medicine, governments are increasingly expecting patients to pay a greater direct share of the drug-cost burden. This can be achieved through the following approaches: 'delisting' or removing from the formulary of older products; introducing or increasing drug co-payments; and allowing a growing number of medicines to be launched with no reimbursement coverage. In the United States, the budgets are shifting in two directions. First, as elsewhere, many patients with insurance coverage are being asked to pay higher co-payments as tiered formularies become the norm. Second, the cost pressure experienced by the increasing Medicare-eligible population (that is, individuals over the age of 65 years) has been translated into political pressure, which has led to a shift in drug funding in the opposite direction — from patients to the government. To optimize strategy from a value and price perspective, pharmaceutical companies need to be aware of the changing roles of the payer, provider and patient in these new models, and to understand how they will affect purchase decisions in the future.

Cost containment has been implemented using many different measures, some of which have a pure cost focus, and others in which the concept of increasing efficiency — or value for the health-care dollar — seems to be the primary goal. Pure cost-control mechanisms include forced rebates, volume caps and price referencing. Efficiency measures include the establishment of higher hurdles to demonstrate added therapeutic value — including the requirement for pharmacoeconomic evidence — as well as increasingly specific treatment guidelines that steer physicians towards the most cost-effective therapies for particular patients<sup>10</sup>.

The move in certain health-care systems towards efficiency and value for money poses both a challenge and an opportunity to drug manufacturers. The challenge is in demonstrating true added therapeutic value, which adds costs to development and raises the bar in terms of which products successfully achieve reimbursement and, accordingly, which products should be entered into development. The opportunity comes in the sense that this focus on overall health-care efficiency signals a move away from the 'silo' view of health-care budgets towards a more integrated perspective. At present, the management of drug budgets continues largely in isolation from other health-care costs. Because of this, the ability to demonstrate health economic benefits and cost savings elsewhere in the system has not automatically been accepted by payers as justifying a price premium for new branded drugs. The increasingly holistic perspective of health-care management provides a more receptive environment for those pharmaceutical companies that are successful in truly demonstrating the health economic benefits of their products.

In countries and health-care systems where cost control remains the priority, with little recognition or willingness to pay for added value, drug companies must consider the commercial benefit of serving these customers or launching in these markets. In New Zealand, for example, which has one of the most restrictive cost-control and pricing systems in the world, several global pharmaceutical companies have gradually reduced their operational infrastructure in response to the increasingly unattractive environment for launching and marketing branded medicines.

On the scientific front, the emergence of pharmacogenetics and the potential for personalized medicine might have a profound influence on the established model for drug development and commercialization, including pricing. The highly targeted nature of these therapies will cause consternation among traditional pharmaceutical marketers, when faced with considerably smaller eligible patient populations than would be the case under the more 'shotgun' approach of classic pharmacology. However, a highly targeted drug will carry a much higher probability of being effective than a conventional drug, and will therefore be of much greater value to its patients and the health-care system. Indeed, in a new model in which a small number of 'blockbuster' drugs are replaced by a large number of personalized medicines, the relative importance of price in maintaining profitability will be even greater than it is now. The challenge will be in demonstrating and quantifying the value of these innovative new therapies in the probable absence of clearly identified pricing references or benchmarks.

Although the future is inherently uncertain, the inevitable demographic evolution towards an older population, combined with an unprecedented rate of technological progress, provides little likelihood that cost pressure on medicines will ease in the near term. The resulting web of globally linked cost-containment measures and health-care efficiency hurdles is equally

unlikely to diminish in either scope or complexity. The ability of pharmaceutical companies to survive and thrive in this environment will rest largely on the understanding and application of the simple concept of value. Although the definition of value is evolving and the measurement systems are growing more demanding, there is little dispute that medicines still represent one

of the most cost-effective elements of the health-care system. Increased focus and investment in conclusively demonstrating such cost-effectiveness, and communicating it broadly, will not only support appropriate pricing and continued profitability of drug manufacturers, but will also serve as an educational platform to help improve the perception of industry.

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#### Competing interests statement

The authors declare **competing financial interests**: see Web version for details.

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