At what price?

Differential pricing could make global medicines affordable in developing countries. But drugs for diseases that have no market in the developed world will require additional subsidies, says **Patricia M. Danzon**.

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For the general population in developing nations to have appropriate access to medicines, existing drugs must be affordable, and innovation is needed to develop new medicines. But this presents a potential conundrum: prices that are high enough to pay for research and development (R&D) may make medicines unaffordable in developing regions. Differential pricing[1] (also known as price discrimination) can offer a solution to this dilemma, at least for drugs with considerable sales in the developed world. Prices in affluent countries — and to a lesser extent in middle-income countries — could generate sufficient revenue to pay for R&D, whereas prices in developing nations need only cover their marginal costs. But differential pricing will be possible only if market separation can be sustained, preventing the low prices in developing countries from spilling over to higher-income nations. However, for drugs that treat diseases endemic only in the developing world, sales are insignificant in the developed world, and additional subsidies are essential to attract R&D for these diseases.

> "Today, R&D costs about US$1 billion for each new drug."

Economics of differential pricing

This prescription of differential pricing and separate markets for on-patent pharmaceuticals is at odds with the free-trade and global-pricing maxims generally favoured by economists. The reason is that R&D costs roughly US$1 billion for each new drug approved in 2007, including the cost of failures and the necessary return on capital invested over the 8–12 years required for R&D[2]. Pharmaceutical R&D can benefit patients globally, raising the question of how this joint cost should be allocated among consumers to generate the greatest benefit. Counting all consumers equally, the answer is that prices should vary inversely with the consumers' price sensitivity — a theory of optimal differential pricing known as Ramsey pricing[3]. Prices must exceed marginal production cost for at least some users in order to pay for R&D. But if all consumers are charged the same price, then the most price sensitive will reduce their use and lose more benefit than would the less price-sensitive consumers. In practice, such sensitivity to drug prices is hard to measure, but a reasonable assumption is that it varies inversely with income. Ideally then, countries with lower per-capita income should be charged less than countries with higher per-capita income.

More generally, economic theory shows that differential pricing promotes greater social welfare than uniform pricing if consumers in aggregate buy more under differential pricing[4] — which seems plausible for pharmaceuticals. A simulation[5] comparing worldwide pharmaceutical prices, revenues and number of consumers served under a single global price with differential pricing between national markets (that is, one price per country) found that differential pricing increases consumer access to drugs by a factor of roughly 4–7 compared with uniform pricing. In addition, differential pricing within, as well as between, countries could significantly increase affordability for poor populations in countries that have a skewed income distribution and no national health insurance. Differential pricing would not only increase the use of existing drugs (static efficiency) but should also increase R&D and the flow of new drugs as a result of increased sales revenue (dynamic efficiency)[6].

A common objection to differential pricing is that it 'shifts costs' between low- and high-priced markets (see ref. 7, for example). But this argument implicitly assumes that the joint costs of R&D should be allocated equally to all users and/or that manufacturers engage in cost-plus pricing, such that if some consumers pay less, others automatically pay more. But, if markets

Out of reach: many medicines are too expensive for people in developing regions.

are separate, manufacturers set the price for each market based on local conditions, irrespective of prices elsewhere. Thus prices would not automatically fall in high-priced markets such as the United States if low-priced markets were to pay more. It is true that if manufacturers were required to charge a uniform price worldwide, prices might drop in the United States because the single price would be based on a weighted average of price elasticities in all the major markets. However, this could be viewed as 'free riding' of high-income, price-insensitive countries on price-sensitive, lower-income countries, and not as the elimination of cost-shifting.

Implementing differential pricing

Although there is widespread support for differential pricing of medicines used to treat HIV/AIDS, tuberculosis and malaria in the lowest-income countries, there is no consensus on applying differential pricing more generally to other drugs and to middle-income countries, or on appropriate benchmark prices and differentials for different countries. Setting benchmark prices based on costs is unworkable because accounting costs do not capture all relevant R&D costs — including failures and the necessary return on funds invested. Moreover, setting prices based on costs creates perverse incentives for producers to inflate costs. More generally, achieving differential pricing through regulation would be vulnerable to political pressures, because underpricing immediately benefits current consumers, but its negative effect on the flow of new drugs is not evident for 8–12 years and will be hard to attribute to specific policies or politicians.

Fortunately, a regulatory structure is not needed to achieve appropriate price differentials. If markets are separate and reasonably competitive, the price differentials that manufacturers would voluntarily charge to maximize profits are similar to the Ramsey optimal price (ROP) differentials required to maximize welfare. Absolute prices may differ, however, because ROP prices are intended to cover costs with a normal return on capital, whereas actual prices can yield positive profits or fail to cover costs, depending on market conditions, competition, regulation and other factors.

Obstacles to differential pricing

Although manufacturers have incentives to pursue differential pricing that is roughly related to per-capita income, the limited evidence indicates that prices are relatively high compared with income in poor countries, making many drugs unaffordable[8,9]. Several factors undermine differential pricing in practice.

Manufacturers adopt differential pricing only if markets remain separate, such that low prices in one market do not erode potentially higher prices in other markets. In fact, such price spillovers occur increasingly, as a result of parallel trade (drug importation by intermediaries, to profit from price differences) and because regulators in middle- and high-income countries use lower foreign prices as an 'external' reference to cap their own domestic prices.

Under traditional patent rules, a patent holder can bar unauthorized importation of a product. However, the European Union has legalized parallel trade between its member states, on grounds of free trade. In the United States, legislation authorizing parallel importation has been enacted but not yet implemented because requirements for quality assurance and cost savings have so far not been met[10]. Although proponents argue that parallel trade is just free trade, in fact parallel trade in pharmaceuticals usually results from differences in price regulation or in per-capita income, and not from lower, real resource costs. Parallel trade, therefore, offers none of the usual efficiency gains from trade; it may, in fact, increase resource costs due to transportation, quality control and relabelling, and reduce welfare gains that would result from differential pricing. Most of the savings accrue to the intermediaries and not to the consumers or payers in the importing country, who continue to pay the higher price.

External referencing can have an even greater impact than parallel trade. It is formally incorporated into drug-price regulation in many countries, including Canada, Greece, Italy, Japan and the Netherlands, and is used informally by many others — including the United States and the United Kingdom, where comparison of international prices frequently informs and influences drug policy. In addition, Brazil has recently demanded the lowest price granted to any other purchasers. With external referencing, manufacturers are reluctant to price a drug cheaply in one country if this would undermine potentially higher prices in other countries. Companies often try to keep the launch price of a drug within a narrow band, preferring to delay or not launch in countries that do not meet the price target[11]. Although

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Differential pricing, coupled with subsidies, could be the key to getting medicines to those who need them.

some middle- and high-income countries may benefit in the short run from external referencing, in the longer term these countries will also be worse off, as the breakdown of differential pricing reduces drug sales and hence leads to less R&D and fewer new medicines.

The distribution of income in many low- and middle-income countries is skewed, causing manufacturers to aim medicine prices at the small, high-income subgroup. Some companies offer discounts to public clinics and other programmes that target the poor, but most governments are unwilling to accept differential pricing within countries. Even where public clinics in principle offer free drugs, many poor people buy medicines from private pharmacies because the clinics are far away, entail long waits or do not have the drugs[12].

Retail drug prices include distribution margins for the wholesaler and pharmacy, which are often higher in poor countries than in higher-income countries that have competitive and technically sophisticated distribution systems, and/or powerful payers to negotiate discounted dispensing fees. Many developing countries impose high import tariffs, inserting an additional wedge between the price paid by the consumer and the price charged by the manufacturer.

Maintaining market separation

Achieving sustainable differential pricing requires market separation, which in turn requires policies and institutions that prevent price spillovers from low-income countries to middle- and high-income countries.

Although the World Trade Organization permits countries to authorize parallel trade, middle- and high-income countries should adopt patent and other policies to bar drug importation, particularly from lower-income countries. It is particularly important that the United States maintains its bar on drug importation. Even if importation is authorized only from high-income countries, enforcement will be unable to prevent importation from other countries if the price differentials offer large profit potential. Legalization of drug importation in the United States would, therefore, increase manufacturers' reluctance to offer low prices elsewhere. Low-income countries should ban parallel exports as far as is legally possible.

Wealthier countries should also forgo formal and informal referencing to foreign prices, including best-price requirements, because these encourage manufacturers to charge more than they otherwise would in low-income countries.

Manufacturers could be encouraged to grant discounts to low-income countries in the form of confidential rebates paid directly to the ultimate purchaser, while wholesalers and other third-party distributors are supplied at a common price. Achieving differential pricing through confidential discounts prevents other purchasers from demanding matched prices or importing the discounted products. Confidential discounts targeted to programmes for the poor could also be used to reduce prices for low-income populations in countries where market prices are high as a result of wealthy subgroups. Providing differential discounts to health plans is standard practice in the United States, where health plans stimulate competition by demanding discounts in return for an increased market share of a drug through preferred formulary placement[13]. Likewise, purchasers for low-income countries could negotiate volume-related discounts payable by electronic transfer, which would effectively link prices to the country's price sensitivity and pre-empt parallel trade and referencing by other purchasers. Confidential discounting encourages competition, whereas publishing bid prices can lead to price inflexibility and tacit collusion between suppliers.

Confidential discounting to implement differential pricing may conflict with policy pressure for price transparency. However, as purchasing on behalf of developing countries is increasingly done either by governments or large non-governmental organizations (NGOs), such as the United Nations Children's Fund (UNICEF), the Global Fund To Fight AIDS, Tuberculosis and Malaria, and the William J. Clinton Foundation, monitoring could be done by audit by an approved third party. Consistent with the thesis that confidentiality ensures the lowest prices, UNICEF does not publish the supply prices of individual vaccine manufacturers. Other NGOs (for example, Médecins Sans Frontières and the Clinton Foundation) have publicized at least some prices, probably to encourage bigger discounts from other suppliers. But, in general, firms that have significant sales in high-income markets are more likely to grant lower prices to developing countries through confidential discounts, rather than to publicly announce price cuts that could trigger matching demands in other middle- and higher-income countries.

Differential pricing through confidential, negotiated rebates is also flexible and could extend over a broad range of drugs and countries. Broadening access to low-priced drugs is crucial in developing countries, given the large and growing burden of chronic disease for which effective medicines exist but are unaffordable without differential pricing.

The World Trade Organization, through the international TRIPS agreement on intellectual-property rights, permits governments to issue a compulsory licence that requires the patent holder to grant a production licence, usually to a local generic company, in cases of national health emergency. Countries with insufficient manufacturing capacity can also issue a compulsory licence to import any medicine[14] — use is not restricted to national health emergencies. A supplementary statement[15] notes the "shared understanding" that the system would "not be an instrument to pursue industrial or commercial policy objectives".

Compulsory licensing reduces prices only if the licensees have lower costs than the originator firms and if they pass these savings on to consumers. However, labour is a small fraction of production cost, and many multinational R&D-based companies have plants in low-wage countries. If originator firms have higher costs, this more probably reflects costs of compliance with environmental and regulatory requirements, including the US Food and Drug Administration. If originator firms charge higher prices than compulsory licensees mainly to avoid price spillovers (which are not an issue for generic manufacturers), this is better addressed by the measures described earlier to assure market separation, rather than by permitting compulsory licensing.

Any short-term benefit to consumers from compulsory licensing must be weighed against the equally real but less visible negative effects of compulsory licensing on R&D incentives. There is a real risk that compulsory licensing could become more widespread, including by middle- and higher-income countries that seek cheaper drugs and/or increased revenue for local firms, at the risk of undermining incentives to develop new drugs in the longer term. This threat would be reduced by effective differential pricing to keep prices low in low-income countries and moderate in middle-income countries.

> "Broadening access to low-priced drugs is crucial."

'Push' and 'pull' subsidies for R&D

Differential pricing can reconcile R&D incentives with affordability in low-income countries only for drugs with significant sales in high-income countries. For diseases that occur predominantly in low-income countries, revenue from drug sales is not sufficient to attract R&D, hence donor subsidies are necessary. 'Push' subsidies fund R&D directly, usually through specialized public–private partnerships aiming to develop new compounds. Advance market commitments (AMCs) are a type of 'pull' subsidy designed to stimulate R&D: donors make a legally binding commitment to pay a specified price for up to a specified number of units of the drug(s) or vaccine(s), which must meet specified criteria, provided that developing countries commit to use the product and pay their share of the price for a number of years. The G8 leading industrialized nations are developing AMCs for vaccines — a pneumococcal vaccine is a candidate in late-stage development, and a malaria vaccine is a possible early-stage candidate. The appeal of AMCs to donors is that they pay only if firms successfully develop the appropriate new medicines, whereas with push subsidies donors pay in advance and bear the full risk of R&D failure.

It is too soon to tell whether AMCs will be effective in stimulating R&D for neglected diseases and at what cost. An analogy is sometimes drawn between AMCs and the orphan-drug laws, which have been very successful. The 1983 US Orphan Drug Act and the similar 2001 European legislation target diseases that affect fewer than 200,000 patients; they combine push subsidies (through R&D tax credits) with a pull subsidy through a seven-year period of market exclusivity. However, the orphan-drug pull component differs from an AMC in that the orphan-drug supplier is free to set the price, and the seven years' exclusivity bars entry by competitors unless they have a differentiated and superior product. By contrast, firms that compete for an AMC face a price fixed by the donors and a significant volume risk, as a result of both market uncertainty (which developing countries will commit to purchase) and market-share uncertainty (which competitors will enter and at what price).

Realistically, AMCs could accelerate the development and diffusion of vaccines that are already in development, but it will be many years before this mechanism is effective at stimulating investment in early-stage R&D. In the meantime, obtaining orphan status in the United States and European Union may provide some additional revenue even for drugs and vaccines that target diseases of developing countries, through differential pricing to the hospital and traveller markets in high-income countries.

Differential pricing could go a long way towards making drugs that are developed for high-income countries affordable in developing countries, while preserving incentives for R&D. But achieving separate markets and eliminating price spillovers across countries is key to achieving differential pricing in practice. This means that middle- and higher-income countries must forgo parallel trade, referencing their prices to prices in lower-income countries, and demanding best-price equalization — practices that would decline if price discounts to low-income countries were kept confidential. If manufacturers sell to distributors at a uniform price but differentiate final prices to purchasers through confidential rebates, opportunities for parallel trade and external referencing are eliminated. If market separation can be guaranteed so that originator firms can sustain differential pricing, then they could charge prices comparable with those of local generic firms in low-income countries, eliminating the case for compulsory licensing.

As differential pricing alone will not stimulate R&D for medicines to treat diseases that occur only in developing countries, supply-side or demand-side subsidies are necessary for such diseases. The optimal strategy would include the use of both, with AMCs as a demand-side subsidy to stimulate commercialization of promising vaccines and drugs that have demonstrated proof of concept. ■

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