Dilemmas In Regulation Of The Market For Pharmaceuticals

In the international pharmaceuticals market, there is little new, and much that is unconsciously replicated, with scant recourse to the evidence base.

by Alan Maynard and Karen Bloor

ABSTRACT: What can be learned from international experience of efforts to control spending and to improve efficiency and access in pharmaceutical markets? Policymakers tend to reinvent many policies to control the behavior of patients, doctors, and industry, despite a lack of evidence of those policies' cost-effectiveness. There is an emerging consensus that reimbursement in public and private health care systems should be informed by evidence of the cost-effectiveness of treatments and that utilization should be constrained by budget caps and information systems. Whatever the policy chosen, evaluation is as essential as it is rare.

DURING THE PAST THREE DECADES, and particularly since publication of Archie Cochrane's book *Effectiveness and Efficiency*, there has been considerable investment in the systematic review of clinical trials of drugs and other treatments, to determine the effectiveness of competing medical interventions.[1] Evidence derived from such work informs, to varying degrees, the regulation of pharmaceuticals at the national level and in individual consultations.

However, "evidence-based medicine" that focuses on evidence of effectiveness alone as the basis for clinical choices is incomplete. A more complete approach is "economics-based medicine," which requires evaluation of both the costs and the benefits of health care.[2] Where health care resources are scarce, decisions based on effectiveness alone do not maximize health benefits for a population and can result in inefficiency and inequity. Economic evaluation may improve health care by including opportunity costs in decisions. Economic frameworks are increasingly having an effect on public reimbursement of pharmaceuticals, particularly in Australasia and Europe.

In this paper we identify policy objectives relating to pharmaceutical markets and review a selection of regulatory interventions. The premise behind the paper is that pharmaceutical markets, like all markets, are always and everywhere regulated, whether by public agencies (government), private agencies (lawyers and

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trade associations), or industry self-regulation. The experience of pharmaceutical regulation implemented in Europe and Australasia provides some lessons for policymakers in the United States and around the world.

Policy Objectives

Regulatory mechanisms are determined by the objectives of regulators. In the market for pharmaceuticals, policymakers—both public and private (for example, managed care companies and other insurers)—generally articulate three objectives: expenditure control, "quality," and "access." Their definition of these goals is often ambiguous, and they rarely rank them or define acceptable trade-offs.

■ **Expenditure control.** In most developed countries, health care spending generally grows at a rate faster than the overall economy. The United States has the most expensive health care system, consuming 14 percent of its gross domestic product (GDP), followed by countries such as Switzerland and Germany, whose expenditure exceeds 10 percent of GDP. Even Britain plans to spend more than 9 percent of GDP on health care by 2008.[3] Controlling overall health spending is a matter of concern to policymakers in tax-financed health systems and in private systems, as costs often fall on employers, thereby influencing their competitiveness.

Spending on pharmaceuticals represents a sizable and increasing proportion of health expenditure, which makes them of particular policy concern. The characteristics of the pharmaceutical markets of selected Organization for Economic Cooperation and Development (OECD) countries over time are shown in Exhibit 1. The United States is a sizable market (despite pharmaceuticals' using a relatively low percentage of the country's health care budget), and markets in France and Japan are also large—approaching 20 percent of their health care budgets in 1998.

EXHIBIT 1
Spending On Pharmaceuticals In Selected Organization For Economic Cooperation And Development (OECD) Countries, 1987, 1992, And 1998

	1987			1992			1998		
Country	Percent of total health spending	Percent of GDP	Spending per capita, in $US	Percent of total health spending	Percent of GDP	Spending per capita, in $US	Percent of total health spending	Percent of GDP	Spending per capita, in $US
Australia	8.1%	0.6%	$ 90	9.9%	0.8%	$143	11.6%	1.0%	$239
New Zealand	14.7	0.9	104	14.2	1.1	152	14.4[a]	1.1[a]	196
United Kingdom	13.6	0.8	107	14.2	1.0	167	15.9[a]	1.1[a]	236
United States	9.3	1.0	186	8.8	1.1	280	10.3	1.3	428
France	–[b]	–[b]	–[b]	20.5	1.5	300	18.5	1.7	391
Germany	14.1	1.3	191	14.2	1.4	260	12.7	1.3	312
Japan	20.3	1.3	185	22.0	1.4	281	17.0	1.2	295

SOURCE: Organization for Economic Cooperation and Development, *OECD Health Data 2002*.
NOTE: GDP is gross domestic product.
[a] 1997.
[b] Data not available.

British, Australian, and New Zealand spending characteristics are modest in comparison, but all are experiencing considerable spending inflation.

Policymakers regard health care spending inflation with concern, be it in the public or private sector. The empirical issue is which mechanisms better create cost control. Do market mechanisms ensure that price and quality competition controls costs and expenditure? Or are global cash-limited budgets, predominantly tax financed with substantial regulation, necessary conditions for cost control? The United Kingdom and New Zealand illustrate the ability to achieve moderate spending growth over time, but they also show that cost control can be undermined by political judgments.

■ **Quality.** *Quality* is an ambiguous term, used in ways that often confuse policy making. Policymakers tend to focus on the structure of health systems, with little evidence on inputs (for example, staffing levels), activities and processes (for example, waiting times), and outcomes of health care. Although the impact of health systems on health can be viewed as a gold standard for policy change, no health care system has routine measurement of broad patient outcomes, using generic measures such as SF-36 or EQ-5D.[4] Even in clinical research studies, health impact is often measured by narrow clinical endpoints, rather than broad impacts on quality of life.

If improvement of the population's health (length and quality of life) is assumed to be the primary goal of a health care system, then by implication high-quality health care is determined by success in improving patients' health status at the least cost. For the pharmaceutical market, this means that cost-effective interventions should be identified for each disease, whether pharmaceutical or not.

Current regulation of the industry requires companies to establish safety, efficacy, and quality (defined as sound manufacturing) of new products for licensing. Efficacy and safety require that clinical trials produce evidence of effect and acceptable side-effect profiles, often compared with placebo. Efficacy is determined by short-term clinical trials prior to market launch, and companies are not generally required to demonstrate relative efficacy (that a new product is superior to existing interventions), although some regulators are moving in this direction.

Products are therefore marketed largely on the basis of efficacy. Systematic measurement of outcome and cost to establish the cost-effectiveness of products is often unavailable. Regulators in Australia, Canada, and some countries in Europe increasingly require companies to provide such evidence for products to be reimbursed by purchasing agencies, supplementing the three existing regulatory "hurdles" of safety, efficacy, and quality with a fourth hurdle, cost-effectiveness.

■ **Access.** *Access*, like *quality*, requires careful definition. Access to drugs is first determined by whether they are included in the benefit package at all. There may be total or partial inclusion, and access also may be limited by user charges (copayments and deductibles). Equity and access criteria may influence the content of lists of reimbursed drugs by the application of often ill-defined criteria (for example, high social values attached to the health of children) and by political choices.

Publicly funded health care systems tend to work with a target of providing equal access to health care for equal need, but, like efficiency and quality targets, this may be a gold standard that is difficult to monitor and achieve.

Regulatory Interventions

Regulation of pharmaceutical markets can be divided into three categories: influencing patients, influencing doctors, and influencing industry.[5]

■ **Influencing patients.** Demand for drugs by patients in Europe has been influenced primarily by user charges. However, recently, the over-the-counter (OTC) market has been developing, and there have been moves toward direct-to-consumer (DTC) advertising. Both influence patients' behavior and require regulation.

User charges and copayments. Practically all countries in the European Union (EU) have user charges for pharmaceuticals, and these can be an important source of revenue. User charge systems vary, but there is little analysis of their relative effects on efficiency, access, and spending. Payments may vary by type of drug (France and Italy), by pack size (Germany), or as a proportion of the cost (France and Spain), or there may be a standard payment (United Kingdom). Exemptions from user charges show similar variety across Europe. Some countries (Germany and Sweden) have ceilings on all charges. Others exempt the poor and elderly (United Kingdom) or particular categories of "essential" drugs (France and Italy).

Evidence about the effects of these systems on utilization and access is limited and tends not to inform political debate. European economists have focused primarily on price elasticity of demand for pharmaceuticals, demonstrating price-sensitivity in response to changing user charges, particularly in poor patient groups.[6] However, evidence from experimental and quasi-experimental studies of cost sharing has come largely from the United States. The RAND Health Insurance Experiment, now more than two decades old, is the most rigorous experimental study in existence.[7] It demonstrates that use of health care is reduced by any form of cost sharing compared with none, although the reduced utilization has no impact on health status. Quasi-experimental studies on low-income (Medicaid) populations have demonstrated reduced use of pharmaceuticals from cost sharing, but with associated adverse health and expenditure effects.[8]

Evidence about cost sharing for pharmaceuticals is consistent across countries and studies in demonstrating that utilization is reduced when patients have to pay. User charges reduce efficient use of pharmaceutical products as well as "unnecessary" care, particularly among low-income groups. There may be a role for user charges in newer "lifestyle" products, but these can be difficult to define and isolate. In general, cost sharing has been as summarized as "misguided or cynical efforts to tax the ill and/or drive up the total cost of health care while shifting some of the burden out of government budgets."[9] In addressing inappropriate prescribing, it may be more suitable to target regulation at doctors, not at patients.

OTC switching. Governments have recently increased the amount of "switching"

of prescription medicines to OTC status. This trend accelerated in the late 1990s in Europe, with consequent cost shifting from government agencies to patients. OTC markets are well established in Germany, France, and the United Kingdom. In the latter, a recent ruling has made price fixing for OTC drugs illegal, encouraging U.K. supermarkets to develop markets for OTC products.[10] This may spread to mainland Europe, where most sales are in pharmacies.

DTC advertising. Advertising of drugs directly to consumers is well established and a matter of continuing dispute in the United States.[11] However, the European Commission is moving slowly to allow it.[12] DTC advertising has been banned in Australia, but such efforts may be limited in the current global economy with wide access to information. The main cause of medical opposition is that it will increase prescribing pressure on practitioners. An investigation of U.S. DTC advertising found that companies spent US$1.8 billion on such advertisements in 1999. The content of 87 percent of the advertisements described benefits in vague, qualitative terms; only 13 percent used data; and none mentioned cost.[13]

Because many efficient drugs are available in relatively cheap generic form (for example, beta-blockers and H2 receptor antagonists) and are unlikely to be advertised, there is a risk that DTC advertising will only be used to market new products, which may be of marginal effectiveness and high cost. This could create expenditure inflation and inefficiency. Careful evaluation of DTC advertising to inform the design of a regulatory framework is necessary but seems unlikely.

■ **Influencing providers.** Physicians are the primary prescribers of drugs, but other health professionals, such as prescribing nurses in the United Kingdom, can determine availability and use. Pharmacists have substantial pharmacological knowledge and experience, which can be used to improve the efficiency of prescribing (for example, by generic substitution). Policymakers in Europe have tended to rely on providing feedback to doctors (such as information on their prescribing behavior and costs and on their generic prescribing rates), hoping that this feedback will influence physicians' behavior. More recently, more prescriptive approaches have been adopted to influence prescribing, including limited lists (formularies), clinical guidelines, and financial incentives.

Information to physicians and clinical guidelines. Marketing of pharmaceuticals is often vigorous and superficial, and it continues to develop, for example, into product endorsement by celebrities in the media.[14] Commercial pressures lead companies to influence or even corrupt the evidence base for reimbursement and clinical decisions, and they compound the choices of prescribers.[15] Pressure from patient and industry lobbies create incentives for doctors to prescribe and systems to reimburse products that do not ensure the most efficient use of society's resources.

It is necessary to distinguish between the hype of drug industry advocates and the evidence of increased effectiveness and cost. A small number of major new products have come to the market in recent decades. The U.S. Food and Drug Administration (FDA) approved more than 1,000 drugs during 1989–2000, of which

361 were new molecular entities (others contained active ingredients already approved) and 153 were selected for priority review.[16] Molecular manipulation is providing products that show marginal improvements in effectiveness, often at a high cost.[17] The industry spends more time and resources to generate and disseminate medical information than it does to produce medicines, and such information can greatly influence clinical practice.[18] Industry's legitimate commercial imperatives and the changes in practice they create can be extremely costly and may undermine the best interests of patients and society. On the other hand, many proven therapies are now off patent, and relatively cheap, but underused because of inadequate incentives that fail to induce appropriate provider behavior.

There are important consequences for the design of clinical practice guidelines, and for information provided to physicians to moderate or even counter the influence of advertising. Guidelines based solely on effectiveness may not achieve efficiency goals: This requires assessment of therapies' relative cost-effectiveness. Policymakers worldwide wish to apply guidelines as a means of making practitioners more efficient. Even in the rare cases where these guidelines affect clinical practice, there may be a risk of increasing inefficiency by distorting overall priorities.[19]

In France, guidelines cover all aspects of medical care and prescribing and are framed as statements about what doctors must not do. In theory, lack of compliance generates a fine related to harm, cost, and the extent of deviance, although most practitioners are not even aware of these rules, and their administration is so complex that they have been little used as control devices.

Prescribing guidelines were also introduced in 1995 in Germany and included a negative drug list. Not surprisingly, these guidelines and the negative list led to a switch of prescribing to newer, more costly drugs but were not the subject of systematic analysis, so the effects on quality, access, and spending are unknown.

Prescribing guidelines are more likely to create behavior change if they are accompanied by additional prompts to change. There is evidence of the effectiveness of policies such as evidence-based outreach, which involves systematic review of the evidence of pharmaceutical treatments, followed by having third parties (such as pharmacists) disseminate this evidence to practitioners. The potential of this approach was demonstrated in the United States decades ago, although the costs of behavior change were not measured.[20]

A recent U.K. study explored the cost-effectiveness of outreach visits to change primary care practice in four areas. Best-practice guidelines were produced based on systematic reviews of the cost-effectiveness of these interventions, and pharmacists were trained to encourage general practitioners (GPs) to adopt these practice guidelines. The effect of such educational outreach by community pharmacists was a modest but significant increase in the number of patients treated within the guidelines, with more change in smaller practices.[21] The change in practice was cost-effective in relation to angiotensin-converting enzyme (ACE) inhibitors, but costs outweighed savings in choice of antidepressants.[22]

Limited lists and generics. A reduction in the number and type of products reimbursed typically creates a one-time impact on spending, but the size of this impact is influenced by the extent of substitution for other medicines. Lists may be "positive," indicating which products will be reimbursed, or "negative," declaring which will not. Definition of these lists is not always related to evidence of even clinical effectiveness, let alone cost-effectiveness. The production of a limited list of cost-effective drugs is a necessary condition to achieving efficiency in prescribing, but unless the use of medicines is monitored, it is not a sufficient condition.

Generic substitution is permitted in six of the fifteen EU member states: Denmark, Finland, France, Germany, the Netherlands, and Spain. Patients' incentives to seek cheaper generic products are limited when copayments are not related to price, so in the absence of generic substitution by pharmacists, doctors must be encouraged to prescribe generically. Generic prescribing is high in some EU countries even without substitution, but it may have modest effects on spending if generic companies are bought out by brand-name producers, to keep prices high.

Budgetary controls. There is limited evidence about the effects of primary care budget holding. In the United Kingdom and Ireland, where GPs were offered the opportunity to economize on prescribing and to use surplus resources in other practice activities, evaluation showed only short-term effects on drug spending.[23]

The potential response of doctors to financial incentives was illustrated by a German policy, which for three years capped overall pharmaceutical spending and announced that the first DM280 million above the ceiling was to be funded out of the doctors' remuneration budget. As a result, the number of prescriptions fell by more than 10 percent in 1992–93, and spending fell by 25 percent.[24] Although prescribing volume later returned to its former level, more permanent savings may have been achieved as "dubious" products were abandoned (saving DM1.8 billion), and a shift to generics saved a further DM350 million.[25]

■ **Regulating industry.** Efforts to influence the behavior of patients and providers are focused largely on the volume of drugs prescribed. Controls on the drug industry itself focus mostly on price, and more recently on cost-effectiveness.

Price controls. Apart from the United Kingdom, where prices are regulated indirectly through a profit scheme, all EU countries have a form of price regulation. In setting prices, these countries use therapeutic comparators and the price of products in other EU markets. Denmark, Greece, Finland, Ireland, Italy, the Netherlands, Portugal, and Sweden set a maximum price in relation to prices in neighboring countries. In Belgium, France, and Italy prices are set in relation to relative cost, prices elsewhere in the EU, and the contribution made to the national economy. In some countries (such as Austria, France, and Spain) there are volume-cost and other rebate schemes. Spain and the United Kingdom set their prices to ensure a rate of return within a particular profit range.

Countries increasingly use reference prices, reimbursing the average price within a therapeutic category. These may reduce price variation across markets

but may also induce inflation in generic prices and reduced competition, as all therapeutic prices are driven to similar levels. In countries such as Germany, Australia, the Netherlands, New Zealand, Sweden, Denmark, and Norway, a decade of reference pricing has achieved only short-term savings.[26]

Price control schemes that do not control volume are incomplete. Physicians control the volume of prescribing, and attempts to limit their discretion have proved ineffective. Whatever the rigor of price control, its effects may be dissipated by volume inflation, which is determined by doctors and influenced by marketing.

Profit controls. The U.K. Pharmaceutical Price Regulation Scheme (PPRS) regulates profits to a band of 17–21 percent on historical capital, with 25 percent variation on either side. Companies are free to set prices, provided their rate of return is within these bands. If profits are higher, the company has to reimburse the National Health Service (NHS) or reduce profits the next year. If profits are lower, the company can raise its prices. This scheme favors domestic companies with high levels of capital in the United Kingdom. It offers little incentive for companies to be efficient, as such behavior reduces costs and raises the rate of return.[27] The transparency of the PPRS is poor, making it impossible to justify the high rate of return offered to the industry. The scheme also produces confusion of goals in government: Industrial policy encourages subsidization of the industry through a high profit level but harms health policy by increasing pharmaceutical spending in the NHS. The resulting "health-wealth trade-off" occurs in many countries.

Cost-effectiveness controls. Throughout the EU and elsewhere, there is increasing interest in complementing pharmaceutical licensing procedures with a "fourth hurdle" of demonstrable cost-effectiveness. Although European economists have advocated such controls for several decades, Australia pioneered the approach nationally within its Pharmacy Benefits Scheme (PBS).[28] Since 1999 the National Institute of Clinical Excellence (NICE) has issued guidance to the NHS in England.[29] Both the PBS and NICE require companies to submit evidence of the costs and effects of new products. Recommendations are generally for specific subgroups of patients and are guided by cost-effectiveness and cost-utility analysis.

Economic data are now used to inform reimbursement and pricing decisions in a number of EU states. Finland, Portugal, the Netherlands, France, Spain, and Sweden are all developing the use of such data in their regulatory systems. Although politicians in some of these states see the fourth hurdle as a spending control, this is generally fallacious, as illustrated by spending inflation in Australia and England. The fourth-hurdle mechanism may increase spending where cost-effective drugs are underused, and it can be used to improve efficiency and equity in drug reimbursement. Increased spending can be health-enhancing if appropriate. Inappropriate prescribing (that is, to groups beyond those identified in NICE or PBS guidance) can be curtailed by compulsory volume controls that reimburse producers at a lower price beyond expected utilization levels. This occurs in some price agreements in Australia, where manufacturers may receive a lower price for a

product if volume predictions are exceeded. However, it is an indirect mechanism for controlling a key problem relating to the partial nature of reimbursement based on cost-effectiveness: Cost-effectiveness varies between patients, and if products are used in broader patient groups than those recommended by bodies like NICE and PBS, spending inflation and inefficiency can result.

Lessons To Be Learned

One lesson to be learned about the regulation of the international pharmaceutical market is that there is little new, and much that is unconsciously replicated, with scant recourse to the evidence base. Policy innovations to regulate the market worldwide have rarely been evaluated scientifically. Exceptions to this are the work of Stephen Soumerai's group in the United States and Nick Freemantle's group in the United Kingdom. The general reluctance to evaluate policy change permits advocates of particular policies to reinvent them, with what Donald Campbell explains as "safety under the cloak of ignorance."[30]

How can pharmaceutical policy better achieve spending, efficiency (quality), and access goals? (1) Many patients do not have access to cost-effective drugs, as a result of consumer, provider, and social choices (for example, exclusion of drugs from benefit packages). Widening access, even if limited to drugs of demonstrable cost-effectiveness, will increase spending. Limiting reimbursement of drugs of dubious cost-effectiveness, and improving prescribing practice with guidelines and volume controls, can finance at least part of this cost.

(2) Pursuit of quality, defined here as the delivery of cost-effective therapies, requires rigorous application of the "fourth hurdle" to reimbursement decisions. Drug reimbursement should be determined by relative cost-effectiveness of new and existing products. Only this will ensure that finite health care budgets are used to maximize improvements in population health status. (3) A common access problem is underuse of available cost-effective drug interventions. Although user charges reduce use, little attention has been given to using incentives to encourage use of efficient treatments by low-income groups, by tested policies that provide incentives to and reward both providers and patients.[31]

(4) Price controls are ubiquitous, but their impact appears to have been slight. Price control must be supplemented with volume control to constrain overall spending. (5) Systems of influencing prescribing by providing information and feedback have had limited success. Guidelines on cost-effective use of pharmaceuticals must be supplemented with incentives and enforced. (6) This requires the management of improved prescribing data, relating diagnosis to treatment and cost-effectiveness and thereby monitoring guideline implementation.

The objectives of spending control, efficiency, and access have to be pursued with separate but related policy instruments. Spending control can be achieved with tax finance and global budgets. Efficiency can be pursued within a macro budget by guidelines, reimbursement rules, and provider behavior that is based on

evidence of cost-effectiveness. Improved access relies on redistributive policies (for example, improving Medicare's benefit package) and improved management to target cost-effective treatment to those who could benefit most. There is much potential for improvement in efficiency and equity in the use of pharmaceuticals, but whatever policies are adopted in this complex market, their costs and benefits need careful evaluation to best make use of society's scarce resources.

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