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Pharmaceutical Pricing Policies in a Global Market
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Chapter 3

Pharmaceutical Pricing and Reimbursement and the Broader Pharmaceutical Policy Environment

The pricing and reimbursement policies used in OECD countries are described and analysed in this chapter. It begins with a description of the coverage schemes that serve to pool risks and defray the pharmaceutical costs borne by individuals. It continues by describing the pharmaceutical pricing schemes employed in OECD countries, including the methods used to limit pharmaceutical prices and define reimbursement price levels. A concluding section provides an overview of aspects of intellectual property rights and marketing authorisation policies that are most important in defining the pharmaceutical policy environment.

Introduction

While each OECD country has a unique mix of pharmaceutical policies, their policy environments share several common features that have important implications for the resulting market dynamics.

First, all OECD countries have established systems of intellectual property rights (IPR) that serve to foster innovation by providing innovators with rights that exclude unauthorised production and sale of an invention for a set period of time. Second, all OECD countries have established regulatory authorities that grant firms the authorisation to market their products on the condition that these meet standards of quality, safety and efficacy. Despite some cross-country variations in IPR and marketing authorisation, the net effect of both these policies is to raise prices by limiting the potential for competition.

Third, in an effort to promote affordable access to pharmaceuticals, all countries have undertaken to subsidise the purchase of pharmaceuticals for some or all of their populations. OECD governments generally treat pharmaceuticals (like health services generally) as a "merit good", whose consumption should not be determined solely by individual preferences and ability to pay (health need is a typical standard by which an individual's pharmaceutical consumption is assessed). Here, there is a great deal of variation among OECD countries, ranging from financing of public clinics providing pharmaceuticals to the uninsured in Mexico, to the tax subsidies for employer-sponsored health insurance benefits in the United States. The net effect is the same: to increase pharmaceutical consumption by reducing or eliminating the direct out-of-pocket cost paid by the consumer.

Coverage schemes

As described in Chapter 1, insurers and public institutions account for most spending on pharmaceuticals, particularly for those medicines dispensed in-hospital and those available by prescription only. Because of their prominence in subsidising pharmaceutical use, coverage schemes play a very important role in influencing pharmaceutical expenditure, price levels and consumption patterns.

The scope of pharmaceutical coverage in OECD countries generally includes medicines dispensed in hospitals as well as medicines prescribed by a physician, although the scope of coverage for in-hospital and out-of-hospital prescription medicines usually differs. In most coverage schemes, medicines furnished during a hospital stay are included in the total charge for the stay.

Some schemes also provide coverage for certain over-the-counter drugs when prescribed by a physician and may also cover self-medication (use of over-the counter drugs without these having been prescribed) under certain circumstances.

Most OECD countries have a common scheme that serves as the primary form of prescription drug coverage for the country's residents. Even where such schemes involve multiple payers, as is the case in Switzerland and the Slovak Republic, they are in essence

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common coverage schemes in that there is little or no permissible variation in the level of drug coverage furnished and the reimbursement prices paid. In some of these countries, a share of the population purchases private health insurance policies that top up existing coverage by subsidising pharmaceuticals not included in the basic coverage scheme (*e.g.,* Switzerland) and covering some or all of the cost-sharing that would otherwise be paid out-of-pocket[1](*e.g.,* Australia, France, Portugal) (OECD, 2004). The extent to which private health insurance finances pharmaceuticals in these countries varies.[2]

Countries that feature multiple forms of basic prescription drug coverage, rather than a single, universal scheme, include the United States[3] and Canada[4], both of which have competing private health insurance plans and publicly financed coverage for eligible population groups. Mexico has several distinct, non-competing social insurance schemes providing coverage for about half the population. Germany has a social insurance scheme that covers about 90% of residents; the remaining 10% opt out and use private health insurance that covers pharmaceuticals and other health care services. There is considerable variation in the extent to which private health insurance finances pharmaceuticals in these countries.[5]

The following sub-sections provide an overview of the key points of differentiation among coverage schemes in OECD countries in terms of:

- the market power of the payers or purchasers,
- the inclusiveness or comprehensiveness of the pharmaceutical coverage,
- the level of subsidy and financial protection furnished,
- the use of benefit management strategies that affect the volume and mix of pharmaceuticals consumed.

Coverage schemes determine the market power of purchasers

A key point of differentiation across OECD countries comes in the policy decision to maximise equity and the prospects for cost control through a common national scheme for pharmaceutical coverage, as has been put in place in most OECD countries, or to maximise consumer choice through a pluralistic system of pharmaceutical coverage. This distinction is important in that the decision largely defines the market power of the payers or purchasers, which is determined by the number of potential customers represented (considered as a share of the total market for a product) and their willingness and ability to pay.

Most types of health care, such as hospital services, are not easily traded across borders. In single-payer coverage systems, purchasers are essentially monopsonists (or in the case of countries characterised by a national health service rather than social insurance, the only provider). As such, they have very significant market power. However, as described in the preceding chapter, the pharmaceutical market is global, with versions of most of the therapeutically important original products sold in most OECD countries. Therefore, no single third-party payer or purchaser of pharmaceuticals can be said to have monopsony power.

Several US purchasers of pharmaceuticals have more market power than do many universal coverage schemes in OECD countries, when measured in terms of population covered and income. The Veterans Health Administration (VHA), for example, one of the largest health care systems in the United States, provides health care to US military veterans. It is financed primarily through general taxation and provides a range of services

including hospital, physician and prescription drug services. In addition to being one of the largest health care systems in the United States, the VHA is also the largest single US purchaser of prescription drugs (IOM, 2000).[6] In 2006, 7.9 million veterans were enrolled with the VA health system (Veterans Affairs, 2006), an enrolment level that exceeds the total population in one third of OECD countries. Beyond this, the largest US pharmaceutical benefits management (PBM) firm,[7] Medco, defines formularies and negotiates pharmaceutical prices on behalf of employers and insurance companies representing 60 million insured people.

Within a country, a system characterised by a single purchaser or payer will have greater power to obtain price concessions from pharmaceutical sellers, as compared to a system in which the national market features multiple schemes operating (and purchasing) independently.[8] However, competing insurers or funds may be able to be more active or discriminating in their purchasing in efforts to meet the demands of those covered, to the extent that those persons are free to choose a competitor – including one that is more or less active in purchasing – if they are dissatisfied.

The comprehensiveness of pharmaceutical coverage varies

A key distinction among coverage schemes is the extent to which they provide coverage for pharmaceuticals available on the market. The most comprehensive schemes, sometimes referred to as "open formulary", cover any drug approved for marketing in the country when it is prescribed by an authorised practitioner. Sometimes, certain categories of products will be explicitly excluded. This type of coverage is also available from some private health insurance schemes that offer primary or supplementary coverage. A variant of this approach – in the sense that all categorically eligible pharmaceuticals are automatically covered upon receipt of marketing authorisation– is the "negative list". Used in very few countries, the negative list indicates which products are not covered (normally this will be an exceptional situation). For example, Germany's social insurance scheme covers all prescription medicines immediately upon market authorisation unless or until they are placed on the negative list. Japan and the United Kingdom also use this approach, as did South Korea prior to 2007.

The most common approach used by third-party payers is to define a list – known as a positive list or formulary – of pharmaceuticals which are subsidised in part or in full. In some cases, virtually all medicines that are proposed for inclusion are included once a decision as to price and/or reimbursement price has been taken.[9] In other cases, purchasers formally select products based on criteria such as effectiveness or cost-effectiveness relative to therapies already covered.[10] In the case of the United States, manufacturers of drugs for which there are therapeutic alternatives often offer payments to PBMs to obtain inclusion on the formularies or to obtain preferred status.[11] In any case, coverage may pertain to all uses of a particular product or be restricted to particular uses (*e.g.,* application as a second-line therapy or limitation to specific target populations). In some coverage schemes, such as the US VHA, selective coverage of medicines and restrictions on coverage are used as a means of managing consumption or controlling costs (see Box 3.1). In other schemes, formularies are comprehensive and coverage of products rarely or never includes restrictions (although other policies may be used to influence consumption of the products).

Some coverage schemes may appear more comprehensive than they are in practice, to the extent that products ostensibly covered (*i.e.,* included on the formulary) are not in fact

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Box 3.1. **Formulary management in the US Veterans Health Administration**

Since 1997, the US Veterans Health Administration has used a National Formulary to help manage its pharmacy benefits. The two main objectives of the National Formulary are to harmonise access to pharmaceuticals across Veterans Administration (VA) regions and to consolidate and maximise purchasing power to negotiate drug prices with manufacturers. The 21 individual Veterans Integrated Service Networks (VISNs) also maintain their own supplementary formularies, and veterans can receive drugs from these formularies as well as the national one.

Following implementation of the National Formulary, the VHA faced criticism that the formulary was overly restrictive, that it adversely affected quality of care, and prevented physicians from meeting the health needs of their patients. The US Congress directed the VA to contract with the Institute of Medicine (IOM) to conduct an in-depth analysis of the effect of the formulary on quality of care, and to compare the restrictiveness, cost and quality of the formulary with other private and government formularies. The IOM concluded that "the VA National Formulary is not overly restrictive. In some respects it is more, but in many respects less, restrictive than other public or private formularies".

National Formulary recommendations are based on drug reviews approved by the US Food and Drug Administration (FDA). Requests for drug or drug class reviews may be made by VISN Formulary Committees and other stakeholders associated with the VA. The VA conducts drug reviews for new FDA-approved drugs focusing on safety and efficacy of the drugs in patient populations similar to the veteran population. VISNs are prohibited from adding new chemical entities (NCEs) to their formularies until the VA has completed a national review. If the VA decides not to list the NCE on the National Formulary, VISNs may still decide to list it on their formularies. If ten or more VISNs add it to their formularies, the VA conducts a new review for consideration of inclusion on the National Formulary.

The National Formulary is partially closed, meaning that not all drugs in particular classes are included and some are subject to restrictions. Listing status generally requires clinical, and increasingly, economic justification. Closed drug classes are major classes that are therapeutically important for the VA population, economically significant, widely utilised and important. Class closures are used as a mechanism to secure lower drug prices (Herdman, 2001), and indeed, substantial price reductions and aggregate savings are typically realised through price-volume contract agreements with manufacturers for drugs included in the closed classes.

Four drug classes were closed in 2000,[1] meaning that the VHA had entered contracts that provide volume-related prices in exchange for committed use, nationwide. Only a few products within a closed class are listed on the National Formulary, and each VISN is required to include these drugs and no others within the class on its regional formulary. A non-formulary exception process exists for patients seeking access to excluded drugs.

The preferred class designation is used to promote the cost-effective use of drugs in a similar, but less restrictive, way. Both steer prescribing and utilisation towards the preferred agents, and both are used to negotiate price-volume agreements with manufacturers. On the National Formulary, two classes are preferred – alpha blockers and calcium channel blockers for treatment of high blood pressure and heart conditions. In these classes, products not designated as preferred products may be used, but prices depend on volume as defined in national contracts.

Box 3.1. **Formulary management in the US Veterans Health Administration** *(cont.)*

In total, the National Formulary generated savings of USD 82.4 million[2] for the five classes that were closed at some point over the IOM study period. Substantial savings were realised through shifts in prescribing behaviour and price reductions from manufacturers. Indeed, the size of the VA population generates considerable bargaining leverage for the VHA when negotiating drug prices with manufacturers, who can expect to secure considerable market share if they are successful in getting their product listed on the national formulary. Conversely, they have much to lose if their product is not listed by the VHA.

The IOM found that larger price reductions were achieved with closed than preferred or open class drugs. With closed class drugs, the price per pill of the most commonly prescribed drugs in the VA system fell by 16 to 41% within three months of a class closure. Overall, most classes remained open as of 2000 (248 out of 254 classes), though it is notable that the four closed classes accounted for approximately 16% of total drug costs in 1998 and 10% of total prescriptions.

1. The four closed classes were: ACE inhibitors, statins, luteinizing hormone-releasing hormone (LHRH) agonists, and proton pump inhibitors.
2. This estimate does not take into account the cost of implementing or managing the formulary – estimated to cost roughly USD 2.9 million over fiscal years 1997-1999.

Source: IOM – Institute of Medicine (2000) and as indicated.

available to patients. For example, availability and accessibility of medicines in Mexico has been hampered by failures of the social insurance schemes and other publicly funded healthcare schemes to keep their pharmacies adequately stocked with products (Moïse and Docteur, 2007a). In the United Kingdom, financial incentives and budget constraints faced by the Primary Care Trusts have been responsible for inequities in access to certain expensive medicines across the country; a phenomenon known as "the post-code lottery" (Walley *et al.*, 2005). Delayed coverage decision-making effectively serves as a form of pharmaceutical benefits management in some coverage schemes. Delays in decision-making may reflect the objectives of cost control, price negotiation or safety considerations. Until recently, US VA policy stipulated that drugs could not be added to the National Formulary until one year after FDA approval.[12] This was designed as a safety-monitoring period in which potential adverse drug reactions could be observed. It was also used to conduct safety, efficacy and cost-effectiveness evaluations of new drugs compared to the most commonly used alternatives (which the FDA new drug approval process does not require) prior to making a formulary listing decision. Following the one-year waiting period, the VA and VISN formulary leaders would work together to make formulary listing and delisting decisions. The VHA faced strong criticism over this policy (Lichtenberg, 2005), and in its comprehensive review of the National Formulary, the IOM found no compelling evidence to support the need for the mandatory wait period. The VA has since abolished it.

Cost-sharing mechanisms

Another key area of differentiation lies in the level at which OECD countries subsidise routine pharmaceutical expenditures and the extent to which they offer financial protection against the risk of incurring high costs associated with the treatment of

catastrophic or chronic illnesses. The key variables are how out-of-pocket spending is determined and whether and how out-of-pocket expenditures are limited.

Most coverage schemes have established cost-sharing for pharmaceuticals, through which patients are required to contribute to the costs of the medicines they use. Cost-sharing requirements are commonly used in coverage schemes to moderate demand for services (by increasing consumer price sensitivity) and shift the burden of financing to patients. In most countries, cost-sharing levels are higher for prescription drugs than for inpatient services or ambulatory care (Docteur and Oxley, 2004). In fact, several OECD countries impose cost-sharing requirements *only* in the pharmaceutical sector. This pattern likely represents policy makers' decisions to vary coverage levels for goods and services to some extent according to the level of patient price sensitivity and consumer discretion associated with consumption of various types of health care.

Coverage schemes vary in the share of the pharmaceutical cost represented by the subsidy. While some schemes (like social insurance in the Slovak Republic) have low or even only nominal pharmaceutical cost-sharing levels, others (like Switzerland and France) subsidise less than three-fourths of the retail price. This results in cross-country differences in the share of expenditures borne by households and contributes to demand for complementary insurance (if permitted). Cohen *et al.* (2006) compared the coverage status of 64 products available in the English National Health Service and in seven major US health plans serving Medicare beneficiaries.[13] About 87% of the drugs were covered, on average, by US drug plans, a share similar to the NHS rate. In the US drug plans, however, pharmaceuticals were subject to deductibles ranging from USD 5 to USD 70 per month, while they were available to patients free of charge in the United Kingdom.

Some forms of coverage include a deductible that must be paid out-of-pocket before the patient is eligible for subsidised pharmaceuticals. Most commonly, the deductible pertains to covered health care generally, rather than to pharmaceuticals specifically.

Cost-sharing may take the form of fixed, or variable, co-insurance rates, or fixed user charges or co-payment amounts. These can vary for different products. For example, in Austria, patients pay a EUR 4 co-payment when purchasing a product that is reimbursed by the social insurance scheme (PPRI, 2007a). In the Slovak Republic, co-insurance rates are variable for different categories of products, ranging from 0% (no co-payment) to 20% (80% of the cost is paid by the social insurance) (Kaló *et al.*, 2008).

The definition of fixed reimbursement amounts for therapeutic clusters

Some coverage schemes define the level of coverage rather than the level of cost-sharing, through the definition of reimbursement limits for classes of bio-equivalent or therapeutically comparable drugs (see Box 3.2). Though such policies are referred to as "reference price policies", they do not directly control the price of the drug, but rather set a fixed reimbursement amount, with patients obligated to pay any difference between the reference level and the retail price of the drug.

The most widely used approach relates to bioequivalent products (same ATC-5 level, *i.e.* same active ingredient or combination of active ingredients), which are placed in reference groups consisting of off-patent products and their generic competitors. In many OECD countries, once a generic competitor enters the market, the reimbursement amount paid by the coverage scheme for the off-patent product is adjusted. For example, the reimbursement level of the off-patent product may be reduced to an amount based on the

Box 3.2. **The use of reference pricing to define reimbursement amounts**

Coverage schemes sometimes use reference prices to set common reimbursement amounts for groups of pharmaceuticals.

Germany was the first country* to employ so-called "reference prices", in which reimbursement of products in a defined group was set at a fixed amount. Since then, several OECD countries have implemented such policies, with specific features in terms of scope (range of products considered for setting reference prices) and reference price setting (the formula used to define the reimbursement level), and the inclusion of patented drugs in the reference price scheme.

Germany introduced fixed reimbursement amounts (*Festbeträge*) for groups of products in 1989. Products are classified according to three levels of "comparability". At the first level, groups are made of products containing the same active ingredient [bioequivalent products, Anatomic Therapeutic Chemical (ATC) classification level 5]. At the second level, groups contain products with pharmacologically/therapeutically comparable active ingredients (ATC 4 level, for example "statins"). At the third level, groups include products with comparable therapeutic effects. *Fesbeträge* are updated on a regular basis, according to a formula taking into account the potential for savings and the number of products available on the market at the proposed price (Le Pape *et al.*, 2000). Initially included in reference price groups, patented drugs were excluded from the scheme in 1995 under industry pressure, but reintroduced in 2004. In 2005, the reference price scheme included products accounting for 60% of the German market (VFA, 2006).

The Netherlands adopted a reference price scheme only a few years after Germany (1991). Products are grouped according to the following criteria: they must have a similar mode or mechanism of action; they must have the same indications for use; there must not be notable differences in properties and adverse effects; they must have the same administration route and target the same population groups (babies, children, adults, older persons). Groups generally correspond to ATC 4 classes or subdivisions thereof. The reference price is determined by successively averaging prices by specialty, by active ingredient, by group and then choosing the price which is just below the computed average unit price per DDD (Le Pape *et al.*, 2000). New drugs are included in a reference group if their producer cannot show evidence that they should not be clustered for clinical reasons.

Following Germany and the Netherlands, many payers and purchasers have adopted a similar approach to defining reimbursement levels. Generally, groups include products with the same active ingredient, but a growing number group drugs that are therapeutic, but not necessary chemical, equivalents.

* The US Medicaid programme, in the state of Maryland, was the first payer to implement reference pricing.

prices of the generic alternatives, leaving patients obliged to pay the difference if they do not switch to the generic product.[14] This is the approach used, for example, in Sweden, where the lowest price-generic alternative is defined as the "reference price", subject to change on a monthly basis (Moïse and Docteur, 2007b).

Several countries – such as Germany, New Zealand and the Slovak Republic – go further, defining certain reference groups (*e.g.*, statins, proton pump inhibitors) on the basis of therapeutic equivalence (products grouped at the ATC-4 level).

Germany has gone even further by classifying certain products that are therapeutically similar, but not equivalent, *e.g.* all anti-depressants have been grouped by the Federal Joint

Commission into a "level 3" cluster. Patented products can be clustered in these so-called "jumbo groups" since 2004 (Paris and Docteur, 2008).

Protection against excessive out-of-pocket expenditure

Patients are sometimes at risk for expenditures associated with a catastrophic illness or accident, in cases where coverage has a defined expenditure limit. For example, a noted feature of the prescription drug coverage in the US Medicare programme is the so-called doughnut hole, which leaves patients liable for 100% of pharmaceutical spending above a certain threshold, with partial subsidies resuming once expenditures reach a higher threshold.[15] Government officials reported that, in 2006 approximately 3 million of 23 million beneficiaries were expected to have reached the point at which the gap in coverage occurred (Lee and Levine, 2006).

On the other hand, Sweden has used a graduated cost-sharing scheme for prescription drugs (excluding inpatient drugs) since 1997. Over the course of a year, patients pay the full cost of reimbursable drugs until they have reached the threshold level in out-of-pocket spending (essentially a deductible). Once the threshold has been reached, patients pay a fraction of the cost of any reimbursable drugs they purchase. The level of the patient co-payment diminishes with the cumulative amount spent until a maximum is reached, above which all pharmaceuticals are provided free of charge to the patient. Families with children under 18 years of age may combine the total cost of all pharmaceuticals prescribed for their children.

Public coverage schemes often employ practices to reduce out-of-pocket expenditures for designated vulnerable groups.[16] Lower cost-sharing or exemptions from cost-sharing requirements are sometimes accorded to vulnerable population groups, particularly for beneficiaries of social assistance, disabled people and those with serious and/or chronic diseases. For example, in Ireland, those certified as having one of several designated long-term illnesses are exempt from cost-sharing requirements for covered medicines (PPRI, 2007e). More exceptionally, cost-sharing levels may differ according to regions, as is the case in Italy (Fattore and Torbika, 2004).

Because the objective of insurance is to defray the costs borne by the patient and protect against burdensome out-of-pocket costs associated with medical need, both public and private payers have an incentive to establish reimbursement prices that include the full contribution from both the payer and the patient (if any), rather than just the subsidy amount. However, there are cases where payers do not seek to constrain sellers to a sales price linked to the reimbursement amount. Such exceptions are normally made to encourage competition on the basis of value among products considered comparable (bioequivalent or therapeutic alternatives), as discussed below. Another approach commonly used to limit out-of-pocket spending is to define or limit the price a seller – manufacturer, wholesaler, pharmacy or all of these components of the supply chain – may charge for medicines that are covered by the payer.

Approaches used to influence the volume and mix of pharmaceuticals consumed

Governments and insurers may seek to influence the volume and mix of pharmaceuticals consumed for a variety of reasons, ranging from cost control to quality improvement. By subsidising expenditure for prescription medicines, health insurance coverage inflates consumption beyond what would be seen in the absence of the subsidy. Coverage schemes in OECD countries differ significantly in the methods employed to

manage the volume and mix of pharmaceutical consumption. Some such policies are geared towards physicians, others pharmacists, and a few directly address patient demand.

Policies geared towards physicians

The ways in which policy makers and insurers try to influence prescribing patterns vary from country to country. In some countries, like Switzerland and Canada, the medical profession itself is considered to be responsible for undertaking any efforts to influence prescribing patterns, and any government initiatives are more geared towards education rather than binding constraints. In these countries, efforts by insurers may be successfully resisted by providers as overly intrusive and inappropriate. In other countries, like Sweden, the health coverage scheme is active – particularly at local levels – in efforts to influence prescribing behaviour.

Sweden is a special case as both local and national governments share responsibility for financing pharmaceuticals and county councils have full responsibility for reimbursing covered medicines. However, the power of these councils is limited as regards the reimbursement list and the price of medicines, thus they try to influence the quantity and type of drugs prescribed. To this end they use Drug and Therapeutic Committees (DTCs), which try to change physician prescribing patterns, and consequently the type and quantity of drugs prescribed. More specifically, DTCs produce lists of recommended first choice treatments and treatment guidelines; and send educators to inform healthcare centres about appropriate use of medicines. The effect of these DTCs is limited, and compliance with recommendations seems to have had an effect only in conjunction with financial incentives (Moïse and Docteur, 2007b).

In an attempt to control rising drug expenditures, Germany introduced collective prescribing budgets in 1993 for all general practitioners in a district. A collective penalty was applied if the budget was overspent. In the years after the introduction of the system, the number of prescriptions, as well as sickness funds' expenditures, decreased. The effect of this measure on quality of care was highly debated. The collective penalties made individual physicians responsible for other physicians' prescribing behaviours, which was seen as unfair. Eventually, the system changed to individual target budgets in 2001, which were, in turn, based upon regional budgets. The effect of this new system, with soft, rather than hard, targets is disputed, based upon evidence from the UK fundholders and indicative prescribing scheme (Walley and Mossialos, 2004). In the Slovak Republic, insurance companies also introduced soft budgets, as physicians resisted hard budgets. Results show little to no effect on prescribing behaviour. Physicians have a different budget target for each insurer they have a contract with, which dilutes the importance of any of the individual budget targets established (Kaló *et al.*, 2008).

Many other types of policies have been implemented in programmes geared at changing the behaviour of providers and pharmaceutical prescribing patterns in order to improve care that would not necessarily be considered strictly as pharmaceutical benefits management (see Box 3.3). In the United Kingdom, where, in 2004, 79% of all prescribed medicines were prescribed using the international non-proprietary name for an active substance, rather than a brand name, a range of policies may have contributed to the outcome, including UK medical school teaching practices and the use of computer software suggesting generic alternatives to branded medicines (Simoens and de Coster, 2006).

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Box 3.3. **Approaches used to influence physician prescribing behaviour**

Clinical practice guidelines are often developed by medical specialists as a guide to physician decision making. Within these guidelines, the overall management of a condition, including best prescribing practice, is proposed. The Canadian Optimal Medication Prescribing and Utilization Service is a programme directed to identifying and promoting best practice in drug prescribing and use, by reviewing and evaluating practice guidelines, rather than developing new guidelines. As the programme has only recently been implemented, it is hard to assess its impact on prescribing behaviour (Paris and Docteur, 2006). In Mexico, the government produced 42 practice guidelines for common diseases, which are not directly aimed at prescribing patterns, but emphasise the use of generics (Moïse and Docteur, 2007a).

Other initiatives used to influence physician prescribing include practice feedback, benchmarking, and continuing medical education (Grol and Grimshaw, 2003; Weiss and Wagner, 2000). Clinical audits and feedback are widely used to assess and stimulate changes in performance regarding guidelines and prescription behaviour. Practice profiling or benchmarking is used in many countries to assess performance of a single provider in comparison with a panel of similar providers. Educational strategies, especially outreach by experts, and mechanisms involving visits and counselling, have proven to be most effective in terms of changing prescribing behaviour (Cantillon and Jones, 1999; Grol and Grimshaw, 2003).

In both Sweden and Switzerland, the pharmaceutical industry and health care professionals adopted a code of good conduct setting forth guidelines and restrictions on education and promotional activities. In Sweden, however, not all county councils have signed the agreement, leading to different levels of co-operation across the country. Some councils have even placed restrictions preventing any direct contact between physicians and the pharmaceutical industry. These county councils should take remedial measures to replace the "educational' role, however biased, of pharmaceutical companies" sales representatives (Moïse and Docteur, 2007b).

In Switzerland, quality circles are the main way in which physician's prescribing is influenced. Quality circles bring together five to eight physicians and one pharmacist on a voluntary basis. These professionals meet regularly to develop collective, evidence-based guidelines, as well as to put these recommendations into practice (Paris and Docteur, 2007). Quality circles have been proven to meet increased quality and efficiency objectives, although the effects on cost savings varied. In addition, participation in these quality circles is validated as part of Continuing Medical Education (CME).

Policies directed towards pharmacists

Many countries have tried to increase the use of generics through generic dispensing policies that allow pharmacists to substitute a generic drug for the prescribed medicine, when the patient agrees and the physician does not object. In most countries that permit generic substitution, physicians can avert substitution by specifying that the prescription should be "dispensed as written". In Hungary, pharmacists are obliged to propose generic substitution, and the proposed substitute must be the cheapest available generic, but the patient has the right to refuse the substitution (PPRI, 2007d). Sweden took generic substitution a step further by mandating substitution by pharmacists of the lowest-cost substitutable product (generic or parallel import) unless a prescription is specified by a physician as "substitution not allowed". The policy seems to have been effective in

generating price competition in the off-patent market and in increasing the market share of generics, and has reduced the average level of co-payments for prescribed medicines (Moïse and Docteur, 2007b). Germany also has mandatory substitution, except where expressly forbidden in writing by the prescribing physician, in cases where the price differential between prescribed product and generic alternative exceeds a certain threshold (ÖBIG, 2007).

The US Veterans Health Administration employs a negative list called the "VA Negative Formulary". It differs from the traditional concept of a negative list, on which listed products are ineligible for reimbursement. Instead, the VA negative formulary lists brand-name drugs for which generic substitution is not permitted, due to concerns with bioequivalence, coding and colour of products or therapeutic equivalence (DVA, 2003). When updated in August 2003, two drugs – Coumadin (warfarin) and Dilantin (phenytoin) – were on the negative list (*ibid.*).

Therapeutic interchange is a commonly applied cost-management tool in the US VHA and is used by about half of US pharmaceutical benefits management firms (Hoadley, 2005). It involves the dispensing of a chemically different drug that is considered to be therapeutically equivalent in that it produces the same therapeutic outcomes and has a similar safety and toxicity profile as the original drug. For example, the therapeutic interchange programme designating lovastatin as the preferred agent within the VHA's statin class came into effect in June 1997. All patients who were taking statins such as pravastatin or simvastatin were switched to lovastatin, the preferred agent. The interchange is reported to have generated equivalent therapeutic outcomes (*e.g.,* cholesterol lowering was the same before and after the therapeutic interchange), equivalent health-related quality of life, and significant cost savings (Patel *et al.*, 1999).

Policies aimed at patient demand

The most commonly used approach to influence patient demand is the cost-sharing requirements used in pharmaceutical coverage schemes. Deductibles and co-payments serve to limit demand by increasing the effective price paid by the consumer. These are sometimes set at one level for all reimbursed products, but are more commonly differentiated, so as to avoid reductions of use of pharmaceutical products considered most important. For example, the Belgian social insurance system defines five categories of medicines, each with a different reimbursement rate (PPRI, 2007b). Those products considered "vital", such as treatments for cancer, are reimbursed at 100% of the price. Products considered "therapeutically important", such as antibiotics are reimbursed at 75% (except for certain vulnerable patients who have an exceptional 85% reimbursement rate). Pharmaceuticals used to treat symptoms are reimbursed at a 50% rate. Similarly, the US private insurer, Humana, also uses a cost-sharing scheme that differentiates products based on type of use, with the lowest co-sharing for drugs that treat acute illnesses and those that are proven to keep patients out of the hospital and the highest for drugs that improve lifestyle with no medical benefit (*e.g.,* drugs for acne, hair loss or sexual dysfunction) (Hoadley, 2005).[17]

Many schemes use differential co-payments to steer use towards products that are less costly for the payer. Most commonly, demand for generics is stimulated by charging differential co-payments for originator drugs (as in Switzerland), or requiring patients who prefer to use an original product for which a generic version is available to pay the difference in price. In the Slovak Republic, the lowest-priced product in a therapeutic group

will be reimbursed at 100% level, whereas other products with higher prices may have co-payments fixed at higher shares (not less than 80%) of the reimbursement price (Kaló *et al.*, 2008). In 2004, 90% of US employees with private health insurance were in plans with a tiered co-payment scheme, of which three-tiered schemes (*e.g.*, generic, preferred and non-preferred drugs) were most common (Hoadley, 2005).

In the US Medicaid programme, dispensing limits, mandated by federal law, are in place to ensure that benefits provided by the different states are "sufficient in amount, duration and scope to reasonably achieve (their) purpose" (Crowley *et al.*, 2005). The three main types of dispensing limits include a restriction on the amount of medication that can be dispensed per prescription, on the number of refills, and on the number of prescriptions per month. The generosity in terms of dispensing limits as well as whether the plan uses hard or soft targets varies widely across the different states. Soft limits are used more often than hard limits, meaning that beneficiaries who have reached their monthly limits are subject to prior authorisation. This gives the beneficiary's provider a chance to provide clinical justification for prescribing above the limit rather than an immediate denial of additional medication.

Prohibition of direct-to-consumer advertising (DTCA) also influences consumer demand for medicines. DTCA is prohibited by law in most OECD countries, although it is allowed in some countries for some OTC medicines. The United States and New Zealand are the exceptions, in that DTCA is permitted for advertisements that meet established regulatory guidelines. Canada has recently revised its policy regarding DTCA, now allowing "reminder ads" as well as "help-seeking ads" (Paris and Docteur, 2006). But the problem of how to properly regulate a mechanism that promotes sales and may inflate prices, but also imparts potentially valuable information to patients, remains.

Pharmaceutical price regulation

Economists know that consumer price sensitivity is low with respect to goods considered necessities, such as pharmaceuticals that are used to combat or prevent a serious illness or debilitating health condition. When the effects of insurance – which reduces the price elasticity of demand for all reimbursed medicines and subsequently increases consumption – are factored in, the demand for pharmaceuticals is "fairly inelastic up to rather high price levels before income effects begin imparting appreciable elasticity" (Scherer, 2000).

Pharmaceutical firms stand to benefit from relatively inelastic demand by pricing at high levels to capture monopoly rents when there is no competition, notably in the case of on-patent medicines for which there is no therapeutic alternative. And even when alternatives exist, competition in pharmaceutical markets is hampered by limits on the information available to those making consumption decisions and by the effects of separating responsibility for the purchasing decision (the physician, in the case of prescription medicines) from responsibility for bearing the cost of the decision (the patient and third-party payer).

Thus price regulation is a policy response to inadequate competition in a market that includes products considered to be necessities and that has been publicly subsidised to avert under-consumption.

Most OECD countries employ either pharmaceutical price regulation or de facto price regulation

The potential for abuse of monopoly power has led two OECD countries with pluralistic coverage schemes – Canada and Mexico – to establish price regulations intended to assure that the prices of patented drugs are not excessive (in Mexico's case this applies to the non-social insurance market only).[18] Their regulations are not linked to any particular coverage scheme or subsidy. Canada's regulation limits the price a manufacturer can charge according to a formula that differs depending on the drug's assignment to one of three categories, based on the extent to which it represents an innovation or improvement over existing products.[19] In its current form, Mexico's price regulation limits the prices paid by consumers that purchase drugs in retail pharmacies to the weighted average of ex-factory prices in the six countries where the product enjoys the highest sales penetration plus estimated (non-regulated) wholesale and retail mark-ups.

Canada's and Mexico's price regulation schemes also serve to offset the market power of monopoly sellers. In Canada's case, numerous private and public plans have not, until recently, sought to engage in active pharmaceutical purchasing strategies or price negotiation (Paris and Docteur, 2006). If price regulation were dropped, payers would likely increase their activity in response to price growth. Conversely, to the extent that purchasers become more active, the rationale for maintaining price control in Canada will diminish. In Mexico's case, half of the population has no coverage for prescription medicines and relies on drugs purchased in retail pharmacies that are financed out-of-pocket (Moïse and Docteur, 2007a). Price regulation thus serves to protect those most vulnerable to the impact of excessively high medicine prices.

In the vast majority of OECD countries, universal coverage schemes act as a combination pharmaceutical subsidy and *de facto* price regulation mechanism that is in effect for subsidised products (whether or not on-patent) nation-wide. This is the case, for example, in Sweden and Switzerland, where pharmaceutical firms submit their proposed ex-manufacturer prices to the pricing and reimbursement authority for consideration with supporting documentation. Once approved, the product is subsidised by the coverage scheme, but the manufacturer may not raise the price without approval; most OECD countries place restrictions on manufacturers' ability to increase prices. Products that are not proposed or approved for reimbursement, including most OTC products, may be sold to consumers in the country at any price.

The US government employs *de facto* price regulation in the case of federal purchasers (*e.g.*, the Veterans Health Administration) and in the Medicaid social assistance programme (Box 3.4) – which provide coverage for about 20% of the US population. These schemes limit the prices manufacturers can charge, using the prices obtained by competing private plans as a benchmark. The US Medicare programme for the elderly and disabled – who are disproportionately heavy pharmaceutical users – does not employ *de facto* price regulation, nor does it use the market power (created by virtue of its coverage of about 14% of the US population) to obtain price discounts. Its market power is decentralised to private plans, whose ability to leverage therapeutic competition has been somewhat curtailed by regulations designed to prevent private plans from risk selection of enrolees that also limit plans' discretion in coverage decisions[20] (Newhouse *et al.*, 2007).

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Box 3.4. **Pharmaceutical pricing in the US Medicaid programme**

Medicaid provides publicly financed health coverage for low-income families with children and low-income aged or disabled individuals. Its enrolment exceeded 55 million, roughly 19% of the US population, in 2003.[1] Approximately 3.6 million were enrolled by virtue of being "medically needy" (those whose disposable income has been reduced by high medical expenses to the extent of meeting Medicaid's financial eligibility test) while the rest qualified as "categorically needy" (low-income persons receiving cash assistance such as supplemental security income) (Crowley *et al.*, 2005).

Financed jointly by the federal and state governments, most responsibility for defining eligibility and service provision criteria, and for administering the programme, is devolved to the states.

While inpatient hospital services, including medications, are part of the mandatory Medicaid benefits package for the categorically needy beneficiaries (but not the medically needy), outpatient pharmacy benefits are not mandatory. All states have opted to provide outpatient pharmacy benefits of some nature, at least for the categorically needy. Most states provide brand name, generic, and some OTC drugs as part of their benefits, but have adopted policies to encourage the use of generic drugs when they are available.

The *Medicaid Drug Rebate Program* requires drug manufacturers who wish to be subsidised by Medicaid[2] to enter into a national rebate agreement with the federal government to provide rebates for outpatient drugs dispensed to Medicaid patients. Manufacturers must agree that the price charged to Medicaid will not exceed the Average Manufacturer Price[3] (AMP) reduced by a rebate percentage. Medicaid law requires states to provide coverage of all FDA-approved medications made by manufacturers who have made rebate agreements.

As of January 2006, the rebate for brand-name drugs is the larger of 15.1% of the AMP per unit, or the difference between the AMP and the best price (BP)[4] per unit and adjusted by the CPI-U based on launch date and current quarter AMP. Reportedly, the rebate given to Medicaid programmes often exceeds 15.1% because of the BP provision (CBO, 2006). The rebate for generic drugs is 11% of the AMP per unit.[5] These rebates are uniform across states and are based on the units purchased.

Supplemental rebate agreements: In addition to the national Medicaid Drug Rebate Program, states may enter into direct price negotiations with manufacturers to secure supplemental rebates. Typically this is done by contracting with a private pharmaceutical benefits manager (PBM), which acts on behalf of the state Medicaid programme to negotiate lower prices from manufacturers. States may negotiate state-specific rebates for their Medicaid population or they may participate in multi-state pooling rebate agreements. With the latter, states pool together their Medicaid beneficiary populations (*i.e.,* total number of beneficiaries) in an effort to increase their purchasing power to negotiate larger rebates and discounts from manufacturers. In 2005, almost half of states received supplemental rebates (Kaiser Family Foundation, 2005).

States are able to negotiate supplemental rebates even though they are required to cover all medicines produced by manufacturers who have made mandatory rebate agreements because they have the authority to restrict coverage. In 2005, preferred drug lists and/or formularies were used in two-thirds of Medicaid plans (Kaiser Family Foundation, 2005). Formulary restrictions vary by state, but exclusions must be justified and excluded drugs must be available through prior authorisation when necessary within 24 hours after request.

Box 3.4. **Pharmaceutical pricing in the US Medicaid programme** *(cont.)*

The state-specific supplemental rebate arrangements implemented in Florida have been recognised as a "best practice" initiative by the US government (HHS, 2004). In 2001, Florida implemented a Preferred Drug List (PDL) in conjunction with state-specific rebates for brand-name drugs. The state's Pharmacy and Therapeutics Committee decides which drug classes to include on the PDL and narrows the list by including only those products that are therapeutically equivalent. Florida's contractor then invites manufacturers to participate in supplemental rebate negotiations of the products within the preferred class. Commencing in July 2004, rebates less than 29.1% of AMP (up from 25.1%) would not be considered by Medicaid for preferred listing status, meaning the drug would likely be subject to prior authorisation criteria. Florida anticipates savings to the tune of USD 24 million from this increase, and does not expect that opposition from manufactures will be substantive enough to threaten the policy change (HHS, 2004).

In 2004, Michigan, Vermont, Alaska, Nevada, New Hampshire, Minnesota and Hawaii received authorisation to enter into a multi-state pooling supplemental rebate agreement. The pooled population consists of approximately 1.1 million Medicaid beneficiaries. Savings ranging from USD 1 million to USD 8 million across states were achieved in the first year, and combined, the supplemental rebate agreement is projected to secure federal savings in the range of USD 19.5 million for fiscal year 2004 (HHS, 2004).

Provisions in the 2005 Deficit Reduction Act (DRA) pertaining to public disclosure of information were intended to improve the evidence base on which states negotiate price agreements with manufacturers, and therefore lead to lower prices. Prior to DRA implementation, manufacturers were required to report their AMP and best price for brand-name drugs to the federal government at the end of each rebate period, with the information protected by confidentiality clauses. The DRA amends this, requiring manufacturers to report their AMP on a monthly basis for both brand-name and generic products. Moreover, as of July 2006, the US Department of Health and Human Services is instructed to report these prices on a publicly accessible website (National Health Law Program, 2006).

Most states differentiate products for coverage and reimbursement by their status as a generic or originator product and implement coverage and reimbursement incentives to encourage the use of generics. Incentives commonly used include charging a lower co-payment for generics, paying a higher dispensing fee to pharmacies that dispense a generic instead of a brand name when possible, paying the generic rate for brand-name drugs, placing generics on preferred drug lists, and taking steps to educate providers about generics (Crowley *et al.*, 2005).

1. By 2005, the Medicaid population had grown to approximately 58.5 million (Crowley *et al.*, 2005).
2. Manufacturers choosing not to participate in the drug rebate programme are not eligible for federal Medicaid coverage of their product(s). Overall, approximately 550 manufacturers and forty-nine states plus the District of Columbia participate in the Medicaid Drug Rebate Program.
3. Average Manufacturer Price (AMP) refers to the average unit price paid to manufacturers for the drug in all states by wholesalers for drugs distributed in retail pharmacies, after deducting discounts. The AMP excludes from its calculation Federal Supply Schedule Prices (Pharmaceutical Pricing Agreement).
4. The best price (BP) is the lowest price paid to a manufacturer for a brand-name drug, taking into account rebates, chargebacks, discounts or other price adjustments. Under the 2005 Deficit Reduction Act, which was implemented in February 2006, generic drugs are now included in the calculation of BP. Prices charged to certain government purchasers are statutorily excluded from best price, including prices charged to the Veterans Affairs and the Federal Supply Schedule (described in chapter text). BP data are not publicly available.
5. Centers for Medicare and Medicaid Services, Medicaid Drug Rebate Program, *www.cms.hhs.gov/MedicaidDrugRebateProgram*, accessed 13 March 2008.

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Market-based pharmaceutical pricing in OECD countries

Throughout the OECD, free or market-based pricing is commonly used in markets for products sold over-the-counter (OTC), with exceptions in cases where OTC products are reimbursed by the coverage scheme. Very few countries regulate the price of patented, non-reimbursed OTC drugs.

On the other hand, there are only three OECD countries (the United States, Germany and the United Kingdom) where pharmaceutical manufacturers are not constrained in establishing their sales prices at market entry.

Although manufacturers in the United States can set list prices for new products freely at market entry, their freedom is checked, on the one hand, by *de facto* price regulation used in certain public programmes, as discussed above, and by competition among insurers in the private sector. In the private sector, the PBMs employed by self-insured employers and health insurance plans use formulary management techniques such as tiered co-payments to influence the mix and volume of consumption, thus giving them leverage to negotiate discounts in cases where products have therapeutic comparators.

In Germany, manufacturers are also free to set their price at market entry. The reference price system is designed to foster price competition among products with therapeutic alternatives. Until 2007, manufacturers faced no regulatory constraint when setting entry prices for new and truly innovative products which could not be clustered with therapeutic alternatives, and health insurance funds were passive payers.[21] However, German authorities have regularly used price freezes, price cuts and mandatory rebates to contain pharmaceutical costs. And the latest reforms seek to promote price competition by strengthening funds' capacity to steer volume towards particular products in exchange for price discounts (Paris and Docteur, 2008).

In the United Kingdom, manufacturers can freely set entry prices of all pharmaceuticals, including those covered by the National Health Service. However, after market entry, pricing is subject to a specific set of constraints due to the Pharmaceutical Pricing Regulation Scheme (see the section on profit control later in this chapter). Beyond profit control at the individual company level, the scheme includes price control mechanisms imposing restrictions on price increases after market entry and regularly entailing across-the-board price cuts. However, by contrast to what happens in other countries, manufacturers are expected to consent to an average price cut (7% in 2007) while retaining some flexibility in the choice of products whose price will be cut (OFT, 2007).

In most of the other countries where free or market-based pricing is possible for prescription medicines, it is allowed only for those drugs which are not reimbursed by the universal coverage scheme. In most OECD countries, this constitutes a relatively small or very small minority of the drugs authorised for sale in the market by prescription, given the importance of coverage to product sales.

Regulators, payers and purchasers use a mix of techniques for defining price levels

Although the motives and rationale for regulating pharmaceutical prices and defining reimbursement prices are different, similar techniques are used in both cases. This section describes the different techniques used to set price limits or reimbursement amounts in OECD countries.

External price benchmarking

External benchmarking of pharmaceutical prices in other jurisdictions is the most widely used technique to limit prices or reimbursement prices in OECD countries. It is perceived by public authorities as a means to assess the fairness or appropriateness of the proposed (or actual) price in relation to what is paid elsewhere.

The use of external benchmarking requires an explicit or implicit notion about how pharmaceutical prices ought to differ across countries, and how they should be similar. The reference pricing policies employed by OECD countries reflect different perspectives on these questions. For example, for its regulation of the prices of patented medicines, Canada selected comparator countries deemed to share its goals of encouraging innovation in the pharmaceutical sector and the domestic presence of a vibrant research-oriented pharmaceutical sector. Mexico uses different comparators for each product, based on the countries with the highest level of sales. The Slovak Republic's comparators also vary by product, as they include the manufacturer's country of origin in addition to countries in close geographic proximity.

Table 3.1 shows that European countries generally refer to each other, *i.e.* they tend to choose countries with similar economic comparability and/or geographic proximity. Austria, on the one hand, benchmarks its prices against the average for the entire European Union – except Bulgaria and Romania (PPRI, 2007a). The Czech Republic, on the other hand, only references Greece, Hungary and Poland (economic and geographic proximity), and Portugal (economic proximity). Despite its economic and geographic proximity, it does not reference the Slovak Republic, even though both countries were once part of the same country.

Germany and the United Kingdom – both of which allow free pricing for innovative drugs at market entry and are often first- or early-launch countries – together with France, are the three countries most commonly referenced. To some extent, this may be opportunistic in that these countries are likely to have prices available for reference soon after first global launch. There are five OECD countries – Australia, Japan, Korea, Mexico and Turkey –not referenced by any OECD member countries.

The way in which the benchmark prices are used also varies across countries. For example, the Slovak Republic sets its price cap at 10% above the average price in the three lowest-priced countries among those referenced. Switzerland is flexible in how the comparator prices are taken into account, disregarding outliers and bringing in alternative countries for consideration when few prices are available.

According to Inazumi (2008), external benchmarking in Japan is used to adjust the price of a new drug if it differs significantly from the average of the drug's price in France, Germany, the United Kingdom and the United States. If the price of a new drug with no therapeutic comparators or a new drug with a significant therapeutic added-value over therapeutic comparators is three-quarters that of the average overseas price, then the price will be increased. If, on the other hand, the price of a new drug, with or without therapeutic comparators, is found to be 1.5 times greater than the average overseas price, then the price will be lowered (Inazumi, 2008).

External price benchmarking is also used by payers within countries, in those countries with pluralistic systems. In Canada, one of the largest provinces, Quebec, requires that manufacturers who wish to sell their products in the province offer the product at the lowest price at which the product is sold elsewhere in Canada (Paris and

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Table 3.1. **The use of external price benchmarking in OECD countries, as of 2007**

Country of regulation	Australia	Austria	Belgium	Canada	Czech Republic	Denmark	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Italy	Japan	Korea	Luxembourg	Mexico	Netherlands	New Zealand	Norway	Poland	Portugal	Slovak Republic	Spain	Sweden	Switzerland	Turkey	United Kingdom	United States	Scope
Australia	–																														Reimbursed drugs
Austria[1]		–																													Reimbursed drugs
Belgium			–																												
Canada				–																											Patented drugs
Czech Republic					–																										Reimbursed drugs
Denmark						–																									All
Finland							–																								All
France								–																							Covered, very innovative
Germany									–																						
Greece										–																					All new drugs
Hungary											–																				All new drugs
Iceland												–																			Prescription drugs
Ireland													–																		GMS-covered prescription only.
Italy														–																	All
Japan															–																Reimbursed drugs
Korea																–															
Luxembourg																	–														Reimbursed drugs
Mexico[2]	Six countries with the highest sales																														Patented drugs sold in the private market
Netherlands																			–												Reimbursed drugs
New Zealand[3]																				–											
Norway																					–										Prescription drugs, covered or not
Poland																						–									
Portugal																							–								Covered drugs
Slovak Republic[4]																								–							Imported drugs
Spain																									–						Covered and non-OTC drugs
Sweden																										–					
Switzerland																											–				Covered drugs
Turkey[5]																												–			Reimbursed drugs
United Kingdom																													–		
United States																														–	

1. Austria benchmarks prices to the EU member states with the exception of Romania and Bulgaria.
2. In Mexico, benchmarking is based upon a voluntary agreement by manufacturers.
3. Comparisons for benchmarking appear to be informal in New Zealand.
4. In the Slovak Republic, the price in the country of manufacture is also taken into account if it is not one of the reference countries.
5. In Turkey, the "country basket" of five comparator countries is chosen every year. The table presents the 2005 situation.

Source: Australia: Sweeny (2004); Austria: PPRI (2007a); Belgium: Eggermont and Kanavos (2005), Mrazek and Mossialos (2004); Canada: Paris and Docteur (2006); Czech Republic: Praznovcova et al. (2003); Denmark: PPRI (2007g); Finland: PPRI (2007h); France: PPRI (2007i); Germany: Paris and Docteur (2008); Greece: Yfantopoulos (2007); Hungary: PPRI (2007d); Iceland: Icelandic Medicines Control Agency (2004); Ireland: PPRI (2007e); Italy: Laux and Gruger (2007); Japan: Inazumi (2008); Korea: Laux and Gruger (2007); Mexico: Moïse and Docteur (2007); New Zealand: PHARMAC (2002); Norway: PPRI (2007j); Poland: PPRI (2007k); Portugal: Laux and Gruger (2007); Slovak Republic: Kaló et al. (2008); Spain: Antonanzas *et al.* (2007); Sweden: Moïse and Docteur (2007); Switzerland: Paris and Docteur (2007); Turkey: PPRI (2007l); United Kingdom: PPRI (2007m)..

Docteur, 2006). In the United States, manufacturers are required by law to furnish their lowest US price to the Medicaid social assistance programme, or to forego sales to a plan serving 55 million people. In addition, the US Federal Supply Schedule (FSS) is a regulated price schedule that requires manufacturers to offer qualified government purchasers their most favoured commercial customer prices, effectively limiting by law the price of brand-name drugs to 76% of the non-federal average manufacture price (Sales *et al.*, 2005).[22] For

about a third of brand-name drugs included on the FSS, a lower price, known as the "Big Four Price" is set for the four largest government purchasers (the Department of Veteran's Affairs, the Department of Defense, the Public Health Service and the Coast Guard) (Roughead *et al.*, 2007).

Internal reference pricing

Internal reference pricing, *i.e.* pricing drugs by reference to therapeutic comparators, is commonly used by payers and regulators to define the price or reimbursement price of certain drugs – most often generic drugs and, less commonly, therapeutic alternatives – at market entry.

While external price referencing, as discussed above, necessarily involves questions about how prices should differ across jurisdictions, internal price referencing also requires difficult decisions – usually implicit – as to how to value differences across products, particularly incremental improvements. In some countries, products representing incremental improvements are not permitted to obtain a premium price over existing therapeutic alternatives. In others, such improvements may be permitted a premium over the price of existing products; however, a key distinction comes in whether the payer pays part of the premium in the form of higher reimbursement price, or whether any premium is to be paid by the patient through additional cost sharing.

The use of internal reference pricing to benchmark the price of original products at market entry

At least four OECD countries (Canada, France, Japan and Switzerland) consider the prices of similar products already on the market – internal price referencing – as a guide to pricing new products that have therapeutic comparators.

In Canada, the PMPRB is in charge of classifying new patented entrants in one of three categories, according to the level of novelty of the new product (see Table 3.2). Only the most innovative products – those classified in Category 2 – will be granted a premium for innovation, *i.e.* a price higher than those of therapeutic comparators. Less innovative products (Categories 1 and 3) must have prices limited to that of pre-existing comparators.

In Japan, the Ministry of Health, Labour, and Welfare is responsible for determining the reimbursement price of drug applications. Drugs deemed to be truly innovative are eligible to receive an Innovativeness Premium which can price it 70 120% greater than the price of a comparator product. Lesser innovative products can be priced 35 60% greater than a comparator product (Usefulness Premium I). Drugs that are considered to have minor therapeutic improvements can still receive a premium price of 5 30% a comparator's price (Usefulness Premium II). Orphan drugs (10-20%) and paediatric drugs (5-20%) are also eligible to receive premium prices

France and Switzerland also consider the degree of new entrants' innovativeness for the purpose of negotiating the prices of new drugs being considered for addition to the positive list. In France, the Transparency Commission (Amélioration du service médical rendu) assesses the therapeutic value of each new drug being considered for reimbursement, as well as its comparative therapeutic advantage over existing alternatives, and rates the degree of a therapy's innovation according to a five-level scale (see Table 3.2).[23] Although products classified in Categories I to IV, *i.e.* presenting some degree of innovativeness in terms of effectiveness, reduction of side effects or patients'

Table 3.2. **Categories used by pricing authorities to differentiate drugs according to therapeutic value**

Pricing authority	Products considered to have high therapeutic value	Products considered to have little or no added therapeutic value, compared with existing therapy
PMPRB (Canada)	Category 2: the first drug to treat effectively a particular illness or one which provides a substantial improvement over existing products (including significant potential cost savings), often referred to as breakthrough.	Category 1: a new Drug Identification Number (DIN) of an existing or comparable dosage form of an existing medicine usually a new strength or existing drug (line extension) Category 3: a new drug or new dosage form of an existing medicine that provides moderate, little or no improvement over existing medicines
ASMR (French transparency commission)	Category I: Major therapeutic progress Category II: Important improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects	Category III : Moderate Improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects Category IV: Minor Improvement in terms of therapeutic efficacy and/or reduction of adverse side-effects Category V: Absence of improvement
Ministry of Health, Labour and Welfare (Japan)	Innovativeness Premium: new drugs that meet the following criteria *a)* clinically useful novel action mechanism; *b)* objectively demonstrated higher efficacy or safety compared with the comparable drug; and *c)* objectively demonstrated improvement in treatment for the disease or injury for which the new drug is indicated. Usefulness Premium (I): a drug that satisfies two of the three requirements for the Innovativeness Premium	Usefulness Premium (II): a drug that satisfies any one of the three requirements for the Innovativeness Premium or is produced using an innovative manufacturing technique that resulted in objectively demonstrated higher clinical usefulness compared with the comparable drug
Swiss Drug Commission	Category (a) Therapeutic breakthrough Category (b) Therapeutic progress	Category (c) Savings compared to other drugs Category (d) No therapeutic progress and no savings Category (e) Inappropriate for social health insurance

Source: Canada: PMPRB (2006); France: Haute Autorité en santé, Commission de la Transparence, *www.has-sante.fr*, accessed 6 July 2007; Japan: Tsumani (2008); Switzerland: Paris and Docteur (2007).

comfort, may claim a higher price than their competitors, products classified in Category V (with no improvement) will be required to offer a lower price than existing comparators to access the positive list.

The Swiss law also refers to a classification of new entrant drugs according to their level of therapeutic novelty and their potential for savings over existing treatment to be used at the time of consideration for inclusion in the positive list (see Table 3.2). The principle for pricing listed drugs is very similar to the French one: Swiss law calls for a premium to be awarded to products defined as innovative, as appropriate. This means that, theoretically, only Categories (a) and (b) are eligible for such a premium. However, in practice, Switzerland's Drug Commission does not undertake formal decisions regarding classification of new entrants and price premiums are reportedly granted to new products which are the first or the second entrant in a therapeutic class.[24] On the other hand, new drugs which are not more effective than existing ones – Category (c) – are supposed to be priced at a lower level if they are to be included in the list.

Both countries make exceptions to this practice, generally allowing the second entrant in a therapeutic class – which does not necessarily offer therapeutic improvement over the first entrant – the same price as the first entrant. In France, any drug following the first entrant in a therapeutic class by less than three years will share the category of innovation assigned to the originator on the grounds that head-to-head clinical trials were not possible due to parallel development of the two products[25]. This provides the Economic Committee for Health Products (CEPS) justification for allowing the subsequent drug(s) to have the same price as the first entrant. In Switzerland, the decision criteria are applied less formally, but the practice is similar. In both countries, subsequent "me-too" drugs with no therapeutic improvements will normally be priced at lower levels.

Generic price linkage

Several OECD countries use internal reference pricing to regulate the price of generic entrants at the time of inclusion in the positive list. Through this practice, known as generic price linkage, the generic is priced at market entry at a discount by reference to the price of the original product.

This practice may be considered as a specific case of the internal price referencing schemes in France and Switzerland, since generics are, by definition, drugs which are not innovative and that should be priced with a discount to be listed for reimbursement. However, in the case of generic price linkage, the amount of the discount is explicitly defined by the regulator.[26] In France, since 2006, generic drugs must be priced at least 50% below the price of the off-patent original. At market entry in Switzerland, generics included in the positive list must be priced at least 30% below this reference price (Paris and Docteur, 2007). In addition, if the price of the originator is lowered at the time of the systematic re-assessment occurring two years later, the price of generic alternatives is supposed to remain at least 15% lower.[27] In any case, if the price of the originator is lowered by its manufacturer, generic manufacturers are not obliged by the law to further reduce their price.

Increasingly, regulators also revise the prices of originals at generic entry; this is the case for instance in Austria, and in France since 2006 (Grandfils, 2007). In France, the CEPS is now supposed to propose a price reduction not only for the off-patent original preparation, but also for other on-patent drugs of the same therapeutic class at the time of generic listing.

Pricing based on pharmaco-economic assessment

Cost-effectiveness analysis[28] and other methods of pharmaco-economic assessment are used to put in perspective the (incremental) cost of a medicine with its (incremental) potential in terms of relevant health outcomes *(e.g.,* improvements in patient health or reductions in disability).

Formal cost-effectiveness studies can be used in two ways to determine whether a product will be reimbursed/subsidised and/or at which price:

- When therapeutic alternatives are available, incremental cost-effectiveness is usually used to make decisions as to whether the new product can be considered "worth" the additional cost.
- When no therapeutic alternative is available, an implicit or explicit definition of a cost-effectiveness threshold is required (Eichler *et al.*, 2004).

Since the introduction in Australia in 1993 of the systematic use of pharmaco-economic assessment in the reimbursement process, most OECD countries use pharmaco-economic assessment in their pricing and reimbursement decisions to varying degrees (Drummond *et al.*, 1999; Dickson *et al.*, 2003; Sorenson *et al*, 2007).[29]

Pharmaco-economic assessment is a technically challenging exercise. Its practice requires a multidisciplinary approach rooted in economics, encompassing a range of disciplines including pharmacology, epidemiology, biostatistics and medicine. This poses problems for smaller or lower-income countries who may not have enough skilled scientists to enable them to carry out systematic pharmaco-economic assessments; for example, in both Mexico and the Slovak Republic, pharmaco-economic evaluations are one

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of several criteria assessed for reimbursement purposes by the respective authorities, yet the resources for properly evaluating these are clearly lacking (Moïse and Docteur, 2007; Kaló *et al*., 2008).

It is very difficult to assess the degree to which countries make effective use of cost-effectiveness analysis. Surveys give some indications (Dickson *et al*., 2003; Drummond *et al*., 2003). In those countries with prominent programmes making use of cost-effectiveness analysis (see Box 3.5), a few key distinctions are evident. First, some programmes take budget considerations in mind as a mitigating factor, influencing the outcome, whereas in other systems, budget considerations are taken into account at other levels *(e.g.,* in developing clinical protocols). Second, most programmes take the perspective of the payer, considering only those costs associated with product use that are borne by the payer, although the Swedish system adopts a broader social perspective. All such systems face a number of important common challenges, including the question of the value assigned to incremental improvements, to what extent to use surrogate endpoints *(e.g.,* tumour shrinkage) in place of outcomes such as improvements in health and disability status, and how to proceed in the face of uncertainty about efficacy.

Payers begin to conclude risk-sharing agreements when evidence of cost-effectiveness is low

Health insurers and public plans seek to obtain maximum value, in terms of health benefits, from their drug purchases. Yet very often, reliable information on the outcomes of a product in general use is unavailable at the time of decision-making. For this reason, an "outcome guarantee", or risk-sharing scheme, provides an attractive approach, particularly where outcomes are in question or the product has a prospectively large cost

Box 3.5. **Approaches used in pharmaco-economic assessment**

Several OECD countries now undertake pharmaco-economic assessment, or closely review the assessments provided by pharmaceutical firms, in the course of pharmaceutical coverage and pricing decisions.

England and Wales implemented pharmaco-economic assessment with the creation of the National Institute of Clinical Excellence (NICE). In England and Wales, new medicines are subsidised by the National Health Service (NHS) as soon as they are marketed, unless they are on a negative list. The mission of NICE is to provide pharmaco-economic assessments and make recommendations on whether the drug should be used or not in the NHS. Studies have inferred from official decisions implicit thresholds at which products are considered cost-effective and found, for instance, that NICE had an implicit threshold ranging from GBP 20 000 to 50 000 per quality-adjusted life year. NICE decisions are binding for primary care trusts and physicians, although the latter retain the responsibility of prescribing appropriate treatments to patients. Positive decisions are sometimes accompanied by additional funding to the NHS to make sure that the new drug is affordable. However, the use of cost-effectiveness is far from comprehensive in the United Kingdom, as NICE does not evaluate all drugs entering the market.

Australia's Pharmaceutical Benefits Advisory Committee serves a function similar to that of NICE, making recommendations as to whether new products should be listed on the positive list used in Australia. In a commentary reviewing studies of NICE and PBAC, Henry *et al.* (2005) noted that the PBAC and NICE appeared to use a similar threshold in terms of cost per quality-adjusted life-year (QALY); however, the PBAC rejects a higher proportion of drug applications with lower cost per QALY values. Possible explanations put forward by the

Box 3.5. **Approaches used in pharmaco-economic assessment** *(cont.)*

authors include a difference in the willingness to accept data known to be error-prone, given that PBAC has direct responsibility for estimating budgetary impacts and recommending prices, which NICE does not.

Canada's Common Drug Review (CDR) is an intergovernmental body which evaluates new chemical entities and new combinations to form an official recommendation as to whether a drug should be included in the formularies of participating publicly-financed drug plans. As of late August 2006, 51 drug reviews have been completed since the CDR's implementation, resulting in recommendations that the federal government, provinces and territories not list in their public drug plan formularies half of the new drugs reviewed (Paris and Docteur, 2006). Some negative recommendations are based on a decision that the product is not cost-effective at the price listed, although the actual cut-off point in terms of QALYs per Canadian dollar (or other metric) is not made explicit. Another important factor is whether surrogate outcomes (such as reduced cholesterol level) are accepted in place of desired health outcomes, such as reductions in morbidity or mortality.

Sweden's Pharmaceutical Benefits Board (LFN) was created in 2002 to decide on inclusion of products in the national positive list at the price proposed by the manufacturer. The question of whether the product is cost-effective at the proposed price is a primary consideration (Moïse and Docteur, 2007b). Incremental cost-effectiveness against prevailing therapy is assessed. Sweden's use of cost-effectiveness analysis is unusual in two respects: First, costs and benefits associated with a product's use are considered from a social perspective, rather than from the perspective of the payer. Second, Sweden employs multiple thresholds at which a product may be considered cost-effective, in order to take into account factors such as the importance of the condition treated by the product for population health and the relative need for a new therapy.

Pharmaco-economic assessment is used by both public and private payers in the United States. About two-thirds of all private health plans used pharmaco-economic assessment in their formulary management decisions in 2004.[1] Among public purchasers of drugs, the Department of Defense's Pharmacoeconomic Center uses pharmaco-economic assessments as part of its formulary management.[2] For the administration of Medicare, in 2007 the Centres for Medicare and Medicaid Services stipulated that pharmaco-economic assessment may be used in formulary management.[3]

Several other countries use pharmaco-economic assessment systematically for informing pricing and reimbursement decisions. In Finland, the Netherlands and Norway, pharmaco-economic assessments are mandatory for reimbursement applications for new drugs. In Belgium, pharmaco-economic assessment is used by the social insurer (INAMI) to evaluate reimbursement applications for new drugs with a therapeutic added-value compared to existing therapeutic alternatives.

Many countries ask manufacturers to submit pharmaco-economic assessments as part of their reimbursement applications, although it is not always clear to what extent this information is used in the decision-making process. Austria, Hungary, Ireland and New Zealand include pharmaco-economic assessments as one of several criteria when deciding on reimbursement applications, whereas in Denmark it is not mandatory, but the manufacturer may submit pharmaco-economic evaluations when applying for reimbursement. Finally, Germany has just recently incorporated pharmaco-economic assessment into its pricing and reimbursement process; an independent body (Institute for Quality and Efficiency in Health Care, or IQWiG) has a legislative mandate to perform pharmaco-economic assessments to inform decisions regarding which health technologies, including pharmaceuticals, should be funded within the statutory health insurance system.

1. According to Cohen (2004), 65% of private health plans in 2004 followed the guidelines for pharmaco-economic assessment as set out by the Academy of Managed Care Pharmacy.
2. See Department of Defense Pharmacoeconomic Center, , *www.pec.ha.osd.mil/mission.htm*, accessed on 29 May 2008.
3. Centres for Medicare and Medicaid Services (2007), *Medicare Modernization Act: Final Guidelines – Formularies*, available at *www.cms.hhs.gov/PrescriptionDrugCovContra/DOWNLOADS/CY07formularyguidance.pdf*, accessed on 29 May 2008.

impact. Under a risk-sharing arrangement, a pharmaceutical company and coverage decision-makers agree on the expected outcomes from a drug in a given indication. If the drug fails to fulfil these expectations, when used under appropriate conditions, the pharmaceutical companies will (partly) refund the health service for the costs (Chapman *et al.*, 2004). Reducing the risk associated with decision-making should make it easier for patients and their doctors to try expensive medicines and make it easier for manufacturers to sell their products (see Box 3.6).

Box 3.6. **Risk-sharing arrangements for pharmaceuticals**

One of the most well-known examples of risk-sharing agreements is the scheme for multiple sclerosis drugs in the United Kingdom. Since May 2002, the NHS has paid for four multiple sclerosis products (Avonex, Betaferon, Copaxone and Rebif) under a risk-sharing scheme. The scheme was agreed after the drug treatments were not recommended for use on the basis of cost-effectiveness grounds by NICE. Under the scheme, the price of the drugs will vary according to evidence regarding its effectiveness derived from patients participating in the scheme. If actual outcomes do not meet expectations, within a margin of tolerance, the company will have to lower the price of the product – which is about USD 20 000 a year per patient.

Another such scheme was introduced on a trial basis in 2000 in the United Kingdom, between the North Staffordshire Health Authority, Keele University and Parke-Davis (now Pfizer), to provide an outcomes guarantee for statins in lowering blood cholesterol concentrations. The scheme was set up after the Health Authority was looking for ways to disseminating best practice for cardiovascular diseases without using excessive resources, or protecting the health service from paying when the drug did not work. At the end of the project all treatment targets were met or exceeded and no refunds made (Chapman *et al.*, 2004).

In the United States, risk-sharing schemes are said to be in development but few specific examples have surfaced publicly. One example is that of Pfizer and Florida Medicaid. They created a risk arrangement in which Pfizer guaranteed Medicaid savings. Pfizer has promised to achieve USD 33 million of savings in a disease management program, in return for inclusion of all of its products on a new restrictive formula (Posey, 2001). Pfizer focused on disease management, including hiring nurses, for high users, who have chronic conditions, such as diabetes, asthma, or heart disease. Pfizer thus takes complete financial risk that the disease management programmes will contribute to reduced health care expenditures.

Other pricing methods used by regulators and payers

Less commonly, regulators and payers in OECD countries use other techniques to limit the prices or set the reimbursement prices of pharmaceuticals.

Passive price taking

Germany is unusual in that the reimbursement level of on-patent pharmaceutical products for which there are no therapeutic comparators is defined according to the list price proposed by the manufacturer without negotiation (*i.e.,* the social insurance scheme acts as a passive price-taker). Coverage is automatic and does not depend on any assessment of value or budget impact.

Profit control as an indirect price control

The United Kingdom uses what amounts to indirect price control by limiting pharmaceutical companies' profits accruing from their operations on UK territory through its 50-year old Pharmaceutical Price Regulation Scheme (PPRS) (see Box 3.7). The dual objectives of preventing any abuse of monopoly position and containing costs in the National Health Service led UK authorities to sign an agreement capping the pharmaceutical industry profits in exchange for a flexible framework for price setting. Manufacturers are free to set the price at market entry. Further increases are limited by the PPRS. If a company's rate of profit exceeds the authorised level, it must reduce the general price level of its products in a manner designed to pay back excessive returns to the NHS, but it remains free to decide on which products will see price reductions as well as to increase prices of other products.

Box 3.7. **The British Pharmaceutical Price Regulation Scheme**

The Pharmaceutical Price Regulation Scheme (PPRS) was implemented in 1957 in the United Kingdom, with the objective of ensuring value for money for the NHS, while at the same time providing the industry with incentives to invest in new and improved medicines.

The scheme has been changing quite considerably over the years (OFT, 2007). Currently the allowable profit is set at 21% return on capital employed and 6% return on sales to the NHS. Maximum margins are allowed before excess profits triggers a rebate to the Treasury or underperformance (minimum margin) may trigger permission to increase prices. The Department of Health (DoH) assesses the company's profit yearly, but only companies with branded sales in excess of GBP 25 million annually are required to regularly submit financial returns (OFT, 2007). The PPRS provides positive incentives for pharmaceutical firms by allowing R&D costs to comprise 20% of UK National Health Services (NHS) turnover, which is higher than worldwide average (Mossialos *et al.*, 2004). Consequently, the PPRS encourages innovation and R&D pharmaceutical investment within the United Kingdom.

The system is positively regarded by many pharmaceutical companies, especially in comparison to alternatives in place in other countries. This is mainly due to the stable and favourable business climate created through a relationship between the DoH and the industry which allows for negotiations of profit margins and other regulatory measures (Mossialos *et al.*, 2004). Furthermore, drugs can be freely launched and priced, after market approval, without any lengthy price negotiations. For the DoH the system is favourable due to the low administrative costs of the PPRS as a team of ten people members operates the scheme with use of minimum resources.

These favourable conditions, however, have been lessened due to frequent price cuts agreed upon during the PPRS negotiations. The companies, however, have some flexibility in deciding which products prices will be cut, known as price modulation. Nonetheless, these cuts have not led to a decline of the rising pharmaceutical expenditure rates, as the increase in pharmaceutical expenditure is attributed to an increased number of prescriptions per head of the population rather than increases in the price of prescriptions (OFT, 2007). This system of price cuts is argued to become part of a strategic game, between the DoH and the pharmaceutical industry (*ibid.*).

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Cost-plus pricing

In some OECD countries, the reimbursement pricing scheme takes production costs into account to set or negotiate prices for certain pharmaceuticals – usually generic versions of original products. This is, for example, the approach used in the Slovak Republic to limit the ex-manufacturer price charged by producers based domestically (exclusively generic manufacturers), and also the approach adopted by Poland. Spain uses a cost-plus approach in which the ex-factory price of a listed drug is determined according to production costs, plus a standard rate of return set at 10 to 12%.

Price-volume agreements

Given the low marginal cost of production, pharmaceutical firms may be willing to negotiate based on the total value of sales, rather than on a per-unit price basis. This prospectively offers lower-income countries a way to provide some access to medicines without potentially compromising the value of manufacturers' sales elsewhere, but there is a need to make sure that products are not diverted to other markets.

Purchasers, public or private, may conclude price-volume agreements at a product level in order to obtain price reductions when volume increases. The French CEPS (see Box 3.8) sometimes enters into so-called volume-price agreements for products with high sales potential, but the "price reduction" takes the form of rebates, paid at the end of the year by the manufacturer with no consequences for the listed price.

Procurement and tendering

Procurement and tendering approaches to pharmaceutical purchasing are used in many countries for purchasing hospital products and by some coverage schemes. However, the case studies undertaken in the course of work on the OECD pharmaceutical pricing policy project revealed that there is little systematic information, even within countries among stakeholders and experts, on the procurement of pharmaceuticals by hospitals for inpatient and outpatient use. This stands to be an important future issue, given growing developments in the area of oncology and other high-cost areas.

In many countries (*e.g.,* Switzerland, Mexico, the Slovak Republic, Canada), hospitals have a certain degree of freedom to devise their own formularies. They may undertake purchasing on an individual basis or collectively, as a way of pooling purchasing power. They may negotiate with manufacturers or wholesalers, or undertake calls for tender for multiple-source products. Manufacturers often provide very heavy discounts, resulting in nearly cost-free medicines, in some cases, as a device intended to induce sales in the retail market (to the extent physicians will decline to switch a patient to another product upon discharge).

Coverage schemes which act as pharmaceutical purchasers, rather than agents that reimburse patients or pharmacies for the products purchased by patients, also use so-called procurement policies, defining the way in which they purchase pharmaceuticals. For example, the US Veterans Administration engages in bulk pharmaceutical contracting with manufacturers in order to standardise benefits across VA regions and to secure price reductions from bulk purchasing. Competitive bidding among brand-name drugs within drug classes is said to be the most contentious, but most important, aspect of VA contracting (Sales *et al*. 2005). Mexico's social security schemes also achieve significant discounts from the retail prices charged in Mexico by using tendering processes to stock the pharmacies and hospitals serving those covered by the schemes (Moïse and Docteur, 2007a).

Box 3.8. **The French State – Industry agreements**

In France, the Economic Committee for Health Products (hereafter CEPS) signs every five years a national "framework agreement" with the pharmaceutical industry association (known as LEEM). This agreement includes commitments from both parties on different shared objectives, such as the exchange of information, a national target for pharmaceutical expenditures (see below), the promotion of a rational use of drugs, and increased use of generic and OTC products. The agreement also states that very innovative products will be priced by the manufacturer, the CEPS retaining the right to oppose the price set if it is not consistent with the price in four EU countries (the United Kingdom, Germany, Italy and Spain) or for public health motives. The CEPS may ask pharmaceutical companies to conduct post-marketing studies to observe how new medicines are used in practice. In case of high risk of misuse and overuse, companies must commit themselves to promote the appropriate use of their products and to be accountable for their promotional activities to the CEPS (CEPS and LEEM, 2003).

The CEPS further signs individual annual agreements with almost all of the companies operating in France. These agreements include information on products' prices and may include provisions linking the price of a specific product to volumes sold, to the "real conditions of use" (for instance, if the average dose prescribed is not compliant with approved conditions for use, the manufacturer will have to pay rebates) or to the average daily cost of treatment (when a drug exists in different dosages and/or formulation, an expected average daily cost should not be exceeded).Individual agreements also include a targeted turnover for current year, beyond which the company will have to pay rebates (CEPS, 2006).

The Parliament annually sets a growth target for manufacturers' revenues drawn from the sales of out-patient reimbursed drugs, beyond which companies will be asked to pay rebates. Then, the Economic Committee for Health Products – the French pricing authority – further defines, in consultation with the industry, how this global target can be differentiated by therapeutic class. A therapeutic class affected by growing clinical needs or by the entry of new products will be allowed a greater targeted growth rate than a therapeutic class in which a leading product will lose its patent or a class whose consumption is deemed too high by health authorities.

For instance, in 2005, the growth target for pharmaceutical industry's revenues in France was +1%. Growth targets for sales of vasodilatators and expectorants were respectively of –15% and –12%, while classes of HIV and hepatitis antivirals and the class containing new drugs to treat rheumatoid polyarthritis and psoriasis were allowed respectively +20% and +121% growth. Since the global target was exceeded in 2005 (sales grew by almost 6%), companies paid 40% of the excess amount, according to a complex formula taking into account their sales in each therapeutic class and the kind of products they sell (innovative and orphan drugs are not "taxable" in the first months after market entry, and generics are never taxable). Overall, the 2005 rebate accounted for 2.3% of the French turnover on reimbursed outpatient pharmaceuticals (CEPS, 2006).

In cases where there is only a single source for a product, procurement policies will not fundamentally differ from policies consisting of negotiating reimbursement prices. There may be two differences: if procurement takes the form of call-for-tender, it will exclude part or all of potential competitors (manufacturers or wholesalers) from the subsidised market; if prices set for reimbursement purposes are often maximum prices – on which

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manufacturers may consent rebates to wholesalers – direct procurement will lead to a fixed price for direct sale by the manufacturer.

All components of the retail price of pharmaceuticals are subject to regulation

Pharmaceutical price regulation schemes generally focus on ex-manufacturer prices

Price regulation schemes (direct or *de facto*) generally focus on defining maximum ex-factory prices of medicines. However, there are some exceptions, such as the Mexican scheme, which addresses the maximum retail price paid by end consumers, and the Slovak scheme, which pertains to the final reimbursement price. In the case of Mexico, with strong competition at the retail level, this means that the impact of any limiting effect of the regulation on prices may fall proportionally more on retailers, than on manufacturers or distributors. In the case of the Slovak Republic, regulating the reimbursement price should be functionally equivalent to regulating the ex-manufacturer price, given that maximum wholesale and retail margins are set in law, and rebates and discounts are prohibited.

From a technical point of view, countries differ in the approach taken for pricing, ranging from linear (in which a product with double the amount of the active ingredient will cost twice as much) to flat (when the price is based on the active ingredient, irrespective of the strength used in the particular product) to regressive (in which products with stronger formulations have higher prices, but the price does not increase in proportion to the increase in strength). All these pricing methods have different implications for outcomes in terms of price levels and in the size of package, formula and strength of dosage that manufacturers will propose to offer on the market.

Regulation of distribution costs is common

Most OECD countries regulate distribution margins by different methods. Regulation of wholesale margins generally takes the form of fixed or capped mark-ups on ex-factory price. Regulation of pharmacists' payments adopts various schemes: fixed or capped mark-up on wholesale price, and/or fixed fees to remunerate pharmacists' services.

The distribution chain faces important regulatory constraints in most countries, ranging from requirements relating to product supply and out-of-hour services to limits in settlements and ownership of establishments. Arrangements for pharmaceutical distribution used within OECD countries will not be discussed here, but regulation of distribution margins is often linked to specific features of the system.

Many OECD countries regulate price increases and try to contain pharmaceutical expenditure growth

Many OECD countries regulate price increases after market entry. In countries with national insurance schemes and positive lists, opportunities for manufacturers to increase prices are very limited. In Switzerland for instance, pharmaceutical companies are required to file an application for any price increase explaining why the price should increase. The United Kingdom, which allows manufacturers to price freely at market entry, does not allow price increases in the following year. In Canada, price increases are limited to inflation. Some countries do not control price increases; this is the case in the United States and Germany.

However, Germany, like other countries has sometimes imposed freezes on price increases in order to contain pharmaceutical costs. Germany is also one of those countries in which policy makers regularly mandate across-the-board rebates to tackle deficits of the health insurance funds. In 2005, manufacturers had to consent to fixed rebates on listed price for a given period (16% in 2005). The rebates applied to products subsidised by the health insurance funds, not private insurers.

Several OECD countries have implemented policies in which manufacturers and/or distributors are required to pay rebates or claw-backs. For instance, in the Netherlands, pharmacists are required to offer discounted prices to their clients, as a policy intended to pass on a share of savings realised in purchasing medicines (PPRI, 2007f). This claw-back takes the form of a fixed percentage discount on retail prices, set by agreement between the ministry of health and welfare and the pharmacists' association.

In France, manufacturers have to pay rebates when the turnover they realise in the French market for reimbursed medicines exceeds the targeted growth rate set by the Parliament. This policy has reached a certain level of sophistication and differentiates rebates to be paid by manufacturers according to therapeutic classes and products' innovativeness, in order to meet public health objectives and to establish what is viewed as an appropriate reward for innovation (see Box 3.8).

Several EU countries have implemented policies to encourage parallel imports as a cost-saving mechanism. For instance, in Denmark, Germany and Sweden, pharmacists are required to inform patients when a less-expensive imported version of a product is available. In Germany, pharmacists are required to replace branded pharmaceuticals with parallel imports when the latter are available at a discount of 15% or more (ÖBIG, 2007). In some countries, pharmacists receive incentives to dispense parallel imports or cheaper drugs; included parallel imported ones (the Netherlands, Norway, Sweden and the United Kingdom). Finally, policies result in lower cost-sharing for patients for the purchase of drugs that were parallel imports in Denmark, the Netherlands and Sweden (Kanavos *et al.*, 2004).

The stability, consistency and predictability of regulation

The pharmaceutical industry puts a great emphasis on the need for stability and predictability of regulation scheme. In this respect, the 50-year old British Pharmaceutical Price Regulation Scheme may be considered as the most stable environment for industry since the rate of profit derived from operations in the British market is not only capped but also guaranteed to a certain extent. The profit cap is negotiated every five years between NHS authorities and the British association of pharmaceutical manufacturers.

Other OECD countries have tried to confer some stability to the pharmaceutical environment through periodic agreements setting the scene for several years. In France for instance, the committee in charge of pharmaceuticals pricing signs five-year agreements with the French association of manufacturers to define shared objectives and to establish principles for price settings and annual rebates calculation (see Box 3.8).

Ultimately, the perceived importance of consistency in application of pricing regulations may strongly depend on the degree to which outcomes of such regulation are perceived as favourable by the industry. In assessments of the reimbursement and pricing procedure made by the two associations representing pharmaceutical industry in Switzerland, representatives of Interpharma, which represents the interests of Swiss companies, described the procedure as "flexible", without indicating that this flexibility

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proved unduly problematic from an industry perspective, whereas VIPS, representing foreign companies operating in Switzerland, indicated that the unpredictability of the system was problematic in some respects (Paris and Docteur, 2007).

Other aspects of the pharmaceutical policy environment that affect the achievement of policy goals

A number of pharmaceutical policies are important in their prospective impact on the timely availability of products in the market, the diffusion of those products and the level of consumption the product will see over its life cycle. Chief among these policies are those that affect market authorisation and those that set standards for enforcement of intellectual property rights.

Intellectual property rights and enforcement

Intellectual property rights have a critical role in the pharmaceutical sector. They guarantee both a period of market exclusivity and a monopoly price through patent rights. They also determine the potential for parallel trade.

Standards and enforcement of intellectual property rights determine the length of time during which a product retains market exclusivity, thus serving as an important determinant of national pharmaceutical expenditures. They play a very influential role in manufacturers' strategic decisions.

While there is some variation in IPR rights and enforcement across the OECD, there has been some harmonisation within the European Union (see Annex 3.A1).

IPR also plays an important role in pharmaceuticals in that it defines, via patent and trademark exhaustion[30] provisions, the opportunities for parallel trade, affecting the ability of pharmaceutical firms to segment the global market through price differentiation (see Box 3.9). As far as OECD countries are concerned, parallel trade is authorised within the European economic area (EAA), *i.e.* European Union plus Iceland and Norway. A derogation on parallel imports from some EU countries was established at the time of their accession to the European Union: Portugal and Spain in 1995 and the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, the Slovak Republic and Slovenia in 2004.

Marketing authorisation policies

Marketing authorisation policies are important in the sense of the timeliness of considering applications and issuing decisions, as well as in their stringency, relative to the other marketing authorities. These two aspects of the policies are important determinants both of manufacturers' strategic decisions with respect to the national market, and of national pharmaceutical expenditures. In both cases, the relevant variable is the total length of time on the market and the period in which an original product has "market exclusivity" before being subject to competition from generic competitors.

Timeliness of market authorisation decisions varies

Figure 3.1 illustrates the average time from application for market authorisation to approval in the 1999-2003 period. It shows that Australia, Canada and Japan had longer delays than their American and European counterparts.

Box 3.9. **Intellectual property rights (IPR) exhaustion regime**

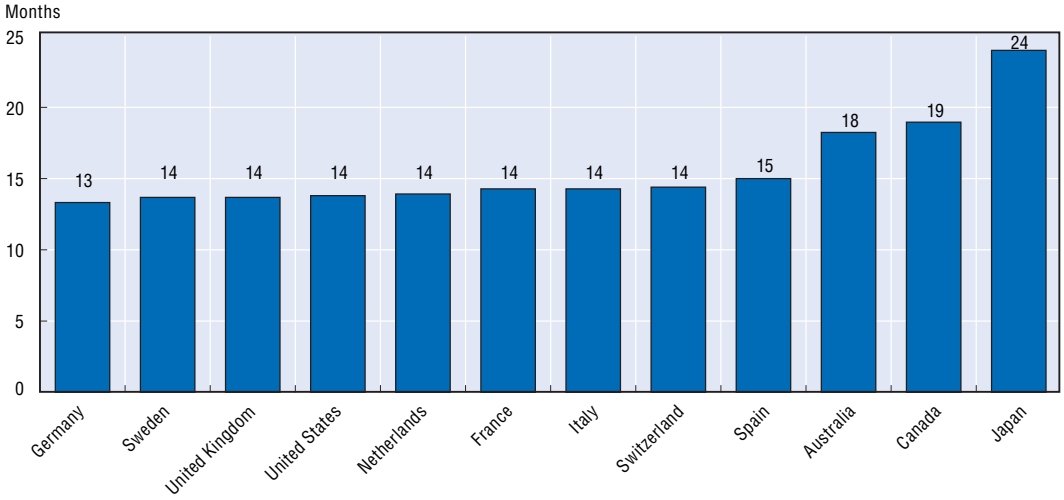
Parallel trade is regulated by general provisions pertaining to intellectual property rights (IPR), exhaustion regimes of the General Agreement on Tariff and Trade and to some limitations of the Trade-Related Aspects of Property Rights (TRIPS) agreement. An intellectual property right (*e.g.* patent or trademark) is said to "exhaust" or end when the patent's or trademark's holder has no more control on its products after the first sale. In such a case, the buyer is free to re-sale the products to anybody at any price. GATT and TRIPS agreement allow countries to define their own exhaustion regimes, unless they have signed bilateral or multilateral agreements with binding provisions on exhaustion regime.

In a regime of national exhaustion, the first sale of the patented or trademarked product by the patent or trademark holder in the country generally exhausts his patent and trademark rights in this country. Subsequently, the buyer may re-sell the product to whoever he wants. Conversely, if the first sale occurs in a foreign country, the patent or trademark holder's rights in the home country might not be exhausted and unauthorised importation of the drugs into the country may infringe upon its patent or trademark. The United States and Switzerland, for instance, have national exhaustion regimes of IPR's rights.

A regime of regional exhaustion means that patent and trademark rights end upon original/first sale within the region (for instance EU), making parallel trade possible, but are not exhausted by first sale outside this region (prohibiting parallel import from countries outside the region).

Under an international exhaustion regime, if a product patented in the country is sold anywhere in the world under either the country's patent or a foreign patent, this exhausts the patent holder's rights under the country's patent. The patent holder cannot restrict importation into the country unless he structures the initial sale in a manner to ensure that exhaustion does not happen, *e.g.* by imposing geographical restrictions on sale. For instance, Canada has a regime of international IPR's exhaustion.

Figure 3.1. **Average time from application for market authorisation to approval, 1999-2003**



Source: Adapted from Pharmaceutical Industry Competitiveness Task Force, Competitiveness and Performance Indicators 2005, indicator 26, from Association of the British Pharmaceutical Industry calculations.

Policies can be used to affect timeliness

Policy makers can take steps to ensure that new products have the potential to be launched on the market quickly by investing adequately in market authorisation reviews to ensure reviews that are both thorough and timely. A well-designed fast-track procedure can aid in moving priority medicines through quickly. In the case of European Union countries, enhanced collective activity (see Annex 3.A2) has meant that market access for some original drugs is no longer as heavily dependent on the capacity of the national authority. However, generic products, many of which are produced for national markets, continue to rely on prompt decisions regarding bioequivalence and substitutability from national market authorities.

Policy changes can increase timeliness of market authorisation decision-making. For example, in 2003, Health Canada launched the Therapeutics Access Strategy, the major focus of which was improving the performance, efficiency and timeliness of the drug review process. As of August 2006, Health Canada eliminated the backlog in pharmaceutical market authorisation decisions and has made progress in meeting internationally comparable drug review targets for pharmaceuticals. Consequently, average and median review times in Canada have declined significantly since 2003 (Health Canada, 2006).

An increased risk of compromised drug safety is a potential consequence of quicker approval times, however. Several studies using US data have examined the relationship between approval times and safety, with mixed results. Friedman *et al.* (1999) and Berndt *et al.* (2005) did not find any association between reduced approval times for Food and Drug Administration (FDA) approved drugs and subsequent withdrawals from market due to safety concerns. Contrary to these findings, a comparison of approval times and drug withdrawals between the United States and Canada found that shorter approval times in the United States were offset by more drugs being withdrawn from market for safety reasons (Rawson and Kaitin, 2003). Furthermore, Olson (2002), using the number of reported adverse events for drugs on the market as an indicator of drug safety problems,[31] showed that shorter FDA approval times were associated with increases in adverse drug reactions leading to death or hospitalisation.

Rudholm (2004) employed the same methods as Olson (2002) for Swedish data to show that shorter approval times for the Swedish Medical Products Agency were associated with more adverse drug reactions, although the effects were considered to be small; a one-year decrease in approval time was associated with an average of between 2.56 and 3.86 additional adverse events.

Responsibility for defining whether generic products can be substituted for originals

In some (but not all) countries, marketing authorisation agencies are responsible for indicating whether generic products can be considered not only bioequivalent, but also substitutable for an original product, taking into account aspects of a product that may affect the relative efficacy of the product. This is the case, for example, in Sweden (Moïse and Docteur, 2007b). Once a generic drug has received approval for marketing in Sweden it is eligible for inclusion in the List of Substitutable Products – the list of generic drugs and parallel imports that can be substituted for the original product under Sweden's generic substitution law.[32] Sweden's Medical Products Agency (MPA) decides whether or not a generic drug will be included in the list. However, the MPA can only initiate the process of

determining if the generic is substitutable after the Pharmaceutical Benefits Board – the agency responsible for determining whether or not a drug will be reimbursed under Sweden's pharmaceutical reimbursement system – has made a reimbursement decision; a process which can take between two and six months. In addition, the manufacturer of the original product can appeal a substitution decision, which automatically removes the generic from the List of Substitutable Products until the courts have resolved the issue. These processes effectively add to the period of the original product's market exclusivity.

Conclusions

This chapter has illustrated that pharmaceutical pricing and reimbursement policies are an important component of the pharmaceutical policy environment, but they are not the only tools by which policy makers affect the price, volume and mix of products used in a country. Subsequent chapters will investigate the role of pharmaceutical pricing and reimbursement policies in contributing to national performance in meeting domestic policy goals as well as external effects.

Notes

1. In Switzerland, such coverage is forbidden by law (Paris and Docteur, 2007).
2. For example, private health insurance finances 18% of pharmaceutical expenditure in France, compared to 3% in both Portugal and Switzerland, even though private policies in the latter are purchased by 80% of the Swiss population (Paris and Docteur, 2007). In Australia, private insurance finances 1% of pharmaceutical expenditure.
3. In the United States, most people have private health insurance coverage that includes coverage for prescription medicines, including medicines furnished in hospital. About 15% (elderly and disabled persons) have coverage through the Medicare social insurance programme, which provides coverage through competing private insurance plans. About 20% (poor) have coverage through the Medicaid social assistance program, which differs by state.
4. In Canada, hospital drugs are covered through the universal Medicare program. Most Canadians have private health insurance, subsidised or organised by their employers, that provides coverage for prescription medicines used outside the hospital. Provinces and territories provide such coverage to seniors, social assistance recipients, and persons with special needs. Federal programmes exist for indigenous peoples and federal government employees.
5. Private health insurance finances about 41% of pharmaceutical expenditures in the United States and about 29% in Canada. In Germany on the other hand, 6% of pharmaceutical expenditures are financed through private health insurance. Mexico is notable in that private health insurance finances only 1% of pharmaceuticals, despite the fact private sources account for almost 90% of pharmaceutical expenditure (Moïse and Docteur, 2007a).
6. The VHA is owned, operated and managed by the US Veterans Administration. This contrasts with the Medicare social insurance and Medicaid social assistance schemes, which reimburse private providers for providing publicly financed medical services.
7. PBMs work with third-party payers (private and some public insurers) to manage drug benefit plans and develop drug management tools. In addition to offering basic services such as claims processing, PBMs also help define which drugs will be paid for, negotiate prices and rebates agreements with manufacturers on behalf of third party payers, and help determine the amounts that pharmacies receive and co-payments consumers pay when prescriptions are filled. Core PBM services include management of formularies, rebate agreements, pharmacy networks, mail-order pharmacy service, claims adjudication, generic substitution, and disease management programmes. PBMs manage pharmacy benefits for over 50% of the total US population with prescription drug coverage, and process prescription drug claims for more than two-thirds of all prescriptions written in the United States (The Health Strategies Consultancy LLC, 2005).
8. Until 1997, the US VHA operated on a decentralised basis, with weaker negotiating powers and "vast" price differences for certain pharmaceutical products purchased by different VA facilities (IOM, 2000).

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9. For example, Switzerland and the Slovak Republic do not exclude any effective medicines that are eligible for coverage (Paris and Docteur, 2007; Kaló *et al*., 2008).
10. This is the case for many of Canada's provincial coverage plans, for example, which exclude products not found cost-effective at the price proposed by the manufacturer.
11. These payments generally take the form of flat allowances, (formulary or access payment) with high variations across drugs and according to restrictiveness of the formulary (higher allowances for being on more restrictive formularies): they vary from 0 up to 27% of total sales (FTC, 2005). Manufacturers' payments may be progressive and linked to the market share, *i.e.* the market share of the drug in its therapeutic class (PBM's prescriptions compared with the national market).
12. The notable exceptions were drugs categorised by the FDA as priority review drugs, meaning that they were believed to offer significant improvement over existing drugs in terms of treatment, diagnosis or prevention of a disease. These were considered on a case by case basis (IOM, 2000). In practice, only new drugs for the treatment of HIV/AIDS were listed before the end of the one-year wait time.
13. The sample included all drugs appraised by the UK National Institute for Clinical Excellence between 1999 and 2005 that were authorised for marketing in the United States. Within each health plan, the authors examined the lowest-premium option offered that used a three-tier formulary, considering that this best represented the coverage furnished to beneficiaries of the Medicare drug coverage scheme. Drugs not included in formularies but whose costs were included in Medicare physicians' payment scheme were considered as covered by the benefit.
14. Most often, there are exceptions in cases where a physician decides that a switch would be problematic for clinical reasons.
15. Medicare pays 75% of initial drug costs up to USD 2 250 after a USD 250 deductible, but then pays nothing until drug expenses reach USD 5 100, after which Medicare pays 95% of all costs.
16. In a review of the literature, Lexchin and Grootendoorst (2004) show that increases in out-of-pocket payments decrease prescription drug use, with potential negative health effects for the poor and chronically ill.
17. Between these extremes are drugs needed to maintain health (such as treatments for chronic conditions) with lower cost-sharing than drugs that boost workplace productivity (*e.g.*, allergy medicines).
18. Switzerland exercises "price surveillance", on the same grounds. All goods and services produced by cartels or firms in monopolistic position (private or public), as well as goods and services subject to government regulation, are monitored by the Price Council. The Council is charged with taking action to hinder excessive prices or excessive price increases and making policy recommendations on regulated sectors. It issues annual reports geared at informing consumers about price levels (Paris and Docteur, 2007).
19. Breakthrough products cannot exceed the median price in seven comparator countries (France, Germany, Italy, Sweden, Switzerland, the United States and the United Kingdom). New formulations of existing products must have a price that bears a reasonable relationship to what is already on the market in Canada. Products that offer moderate, little or no therapeutic advantage over existing products are limited to the price of the comparable products on the market. Price increases are limited by growth in the consumer price index.
20. For example, the requirement that plans must list "all or substantially all" of the drugs in the antidepressant, antipsychotic, anticonvulsant, anticancer, immunosuppressant and HIV/AIDS categories has generated controversy (McAdams and Schwarz, 2006). Participating plans argue that offering a limited formulary provides them with bargaining leverage to negotiate price reductions with manufacturers. When many drugs within the same class are listed, their bargaining leverage declines.
21. Things may change with the introduction of cost-effectiveness assessment and maximum reimbursement prices in the 2007 reform (Paris and Docteur, 2008).
22. US purchasers eligible to use the Federal Supply Schedule can and do negotiate prices that are lower than what appear on the Federal Supply Schedule, however, using techniques such as blanket purchase agreements (BPAs), under which the purchaser agrees to purchase only from a particular supplier.
23. The Transparency Commission is composed of clinical experts and is part of the High Authority on Health.

24. The premium generally amounts to 10 to 20% of the price of therapeutic comparators, when there are any, but premiums granted to breakthrough drugs are not limited in this respect. Higher premia may be awarded for drugs with limited market potential, such as orphan drugs (Hunkeler, 2006).
25. See Réglement intérieur de la Commission de Transparence du 22 June 2005.
26. By contrast, no minimum discount is set for non-generic drugs with no therapeutic improvement over existing comparators.
27. Swiss policy makers intend to reform this system so that, in the future, regulation of generic prices will occur only at market entry.
28. Cost-effectiveness analysis is the most commonly used form of pharmaco-economic assessment. Other techniques, such as cost-benefit analysis or cost-utility analysis, might be used under certain circumstances (Dickson *et al.*, 2003).
29. Information on the use of pharmaco-economics for most OECD countries is also available from the International Society for Pharmacoeconomics and Outcomes Research (*www.ispor.org/peguidelines/index.asp*).
30. The term "exhaustion of patent or trademark rights" refers to a provision of intellectual property law that defines the conditions under which patent or trademark owners' rights expire. For example, a regime of regional trademark exhaustion means that the trademark owner forfeits control over the re-sale of its products within a given region once he has sold them. This provision allows parallel trade in Europe.
31. Using adverse drug reactions (ADRs), as opposed to drug withdrawals, lowers significantly the statistical variation because there are significantly more reported adverse events – 16 148 ADRs requiring hospitalisation and 5 243 leading to death in the Olson study – than there are drug withdrawals – 22 in the Berndt *et al.* study.
32. Sweden's generic substitution law stipulates that a pharmacy is obliged to substitute the cheapest generic drug available for the prescribed product.

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ANNEX 3.A1

Pharmaceuticals and Intellectual Property Rights in the European Union

Patents

There is no single, centrally enforceable EU-wide patent. A European patent refers to patents granted by the European Patent Office (EPO). Under the European Patent Convention (EPC) treaty, the EPO provides a single, harmonised procedure for granting patents in the European Union. Applications can be made in one of the official languages of an EPC contracting state to the EPO's offices in Munich, but processing of the patent is done in one of the three official languages of the EPO (English, French and German).The applicant designates which EPC countries it wishes to file for patent protection. A favourable decision by the EPO grants a patent in each of the designated states. However, the determination of ownership, validity and infringement are subject to respective national laws. Furthermore, while a national court may invalidate a patent in one country, the European patent remains valid in the other designated countries. A European patent is, in effect, non-unitary across all EU countries and independent in each.

The EPC does impose some limits on its signatories. The basis for determination of validity of a patent by national law is limited to a few reasons, but the standard on which the determination is made is that of national law. The convention also requires all jurisdictions to give a European patent a term of 20 years from the filing date, either the date of filing with the EPO for a European patent or for an international application under the Patent Cooperation Treaty.[1]

Supplementary Protection Certificate

A holder of a pharmaceutical patent still in force in the European Economic Area can apply for a supplementary protection certificate (SPC), an extension of rights for said patent. An SPC is a unique, patent-like IPR that comes into force after the patent expires, for a maximum period of five years. There is no single European SPC; applications are made on a country-by-country basis. The term of the SPC depends on the time between patent application and granting of marketing authorisation.[2] An SPC is a tool governments use to compensate manufacturers for the lengthy period of time it sometimes takes for granting marketing authorisation, however it does delay the entry of generic drugs onto the market.

Bolar provision

The so-called Bolar provision[3] of the Hatch-Waxman Act, enacted by the US Congress in 1984, granted drug manufacturers the right to "make, use, offer to sell, or sell … a patented invention" for uses related to submission of information under Federal law regulating drugs.[4] The use by generic manufacturers of pharmaceuticals still under patent protection for the purpose of submitting information to regulatory agencies for obtaining marketing authorisation has, until recently, been governed in Europe by each member state's national law.

The European Commission (EC) concluded that a provision for generic manufacturers similar to the Hatch-Waxman Act should be permitted for all member states. In 2004, the EC revised Directive 2001/83/EC on the Community code relating to medicinal products for human use, to include the following amendment:

> "Conducting the necessary studies and trials … and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."[5]

Member states had 18 months from April 2004 to implement the Directive into their national laws.

The amendment clearly allows the use of on-patent medicines by users other than the holder of the patent for "conducting the necessary studies and trials" for "consequential practical requirements", but left uncertain the legality of other actions, such as supplying or exporting on-patent medicines to generic manufacturers. By using the ambiguous wording "consequential practical requirements", the EC has apparently left the interpretation to national courts (Ashurst, 2005).

Data exclusivity

Complementary to Bolar provisions are legislation that protect the clinical trial data that original product manufacturers are required to submit in their applications to regulatory agencies for marketing authorisation. The original product manufacturers argue that such protection is necessary; otherwise they are at an unfair disadvantage since generic producers can use these rather expensive data at no cost. The generic producers reply that not having access to these data act as a restriction on producing generic products, thereby limiting the availability of cheaper alternative pharmaceuticals.

One of the European Commission's amendments to Directive 2001/83/EC revised EU aspects of data protection. It provided that test data supplied by the manufacturer of an original product, as required by marketing authorisation legislations, are protected for a period of eight years following the first marketing approval in a member state. This period of protection is followed by a two-year period during which generic versions of the original product may not be launched on the market of any member state, although marketing authorisation can be granted during this period. Finally, the original producer can obtain an additional one-year period of market exclusivity beyond the two-year period if, during the eight-year data exclusivity period, the producer obtains marketing authorisation for additional indications which bring a substantial clinical benefit compared with existing therapies. In effect, this new regulation creates the so-called "8 + 2 + 1" formula which guarantees the original producer a period of market exclusivity equivalent to ten years, with the possibility of extending that exclusivity to 11 years (Sanjuan, 2006).

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Member states had until 30 October 2005 to implement the new Directive. In the face of opposition to the new law from prospective member states who were not able to vote on it, these states can request derogation. The law came into full effect in November 2005, meaning that the first generic drugs to be affected by this law will not come on to the market in the European Union until 2015.

Notes

1. The Patent Cooperation Treaty provides a unified procedure for filing patent applications.
2. For the purpose of granting an SPC, marketing authorisations granted in Switzerland are also considered since Liechtenstein automatically accepts authorisations granted in Switzerland.
3. In 1984, Roche Products Inc. sued Bolar Pharmaceuticals Corp. Inc. for violating its patent for flurazepam-HCI. Bolar had obtained some of the active ingredient from a foreign manufacturer and had started the bio-equivalency studies necessary for obtaining marketing approval for a generic version of Roche's patented product, prior to the patent's expiration. A court of appeal overturned a lower court's decision, saying that Bolar had violated Roche's patent. This judgment meant that generic manufacturers could not conduct bio-equivalency studies for obtaining marketing authorisation until the patent of the original product expired.
4. Drug Price Competition and Patent Term Restoration Act [Public Law 89-417, 35 USC. paragraph 271(e)(1)].
5. Directive 2004/27/EC, Article 10(6), 31 March 2004.

ANNEX 3.A2

Marketing Authorisation in the European Economic Area

Authorisation for marketing a medicine within the European Economic Area (EEA)* is granted through the competent authority of any EEA country – valid within the particular country – or through one of the recognised procedures for obtaining authorisation in more than one EEA country. The holder of a marketing authorisation valid within the EEA must have an established presence within the EEA.

The London based **European Medicines Agency (EMEA)** was established in 1995 to coordinate the evaluation and European market authorisation for both human and animal medicinal products. The EMEA operates under the aegis of the European Commission's DG Enterprise, to which it forwards its opinions for approval for final marketing authorisation in all member states.

There exist three procedures for obtaining marketing authorisation in more than one EEA country: the centralised procedure, the mutual recognition procedure, and the decentralised procedure.

The **Centralised Procedure (CP)** is used to obtain a marketing authorisation valid in all EEA countries. The procedure is mandatory for, but not limited to, biotechnology, AIDS, cancer, diabetes, neurodegenerative disorder medicines as well as orphan drugs. Applications submitted to the EMEA by manufacturers are evaluated by the Committee for Proprietary Medical Products (CPMP) – comprised of two experts nominated by each member state. The CPMP subcontracts the assessment to two rapporteurs selected from a pool of 3 500 drug evaluation specialists in national regulatory agencies. The CPMP has 210 days from receipt of the dossier to provide a recommendation to the European Commission for final approval; however the clock can be stopped when rapporteurs request additional information from the applicant. Total accumulated time during which the clock is stopped generally should not exceed six months.

The Decentralised and Mutual Recognition procedures are based on the principle of recognition by other member states of a first approval granted by the authorities of one member state.

Through the **Mutual Recognition Procedure (MRP)**, manufacturers can apply for marketing authorisations in designated "Concerned Member States" (CMS) by validating the marketing authorisation *previously granted in another member state* – the "Reference Member State" (RMS). The competent authority in each CMS has 90 days in which to decide

* The EEA is composed of the 27 European Union member countries plus Norway, Iceland and Liechtenstein.

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whether it agrees with the RMS' marketing approval decision. In case of disagreement, the RMS sends the concerns to the CPMP; if a consensus is not reached after a further 60 days, the procedure moves into arbitration by the CPMP.

The **Decentralised Procedure (DP)**, introduced in 2005, increases the EMEA's co-ordinating role to facilitate the harmonisation of marketing approvals. Manufacturers of new products *not yet marketed in one of the EEA member states* (and not obliged to use the CP), as well as generic versions of original products authorised through the CP, designate a Reference Member State to undertake the assessment. Identical dossiers are submitted to Concerned Member States where approval is also sought. The RMS steers the approval process, seeking agreement on elements that must be harmonised in CMSs and provides a decision. A maximum of 210 days is granted (including a maximum of three months for clock stops to allow for applicants to respond to objections raised during evaluation) to the RMS and the CMSs to come to an agreement on the full dossier. If agreement is not forthcoming then an additional 90 days are granted for arbitration, with a final decision by the CPMP. The recommendation is then forwarded to the European Commission for final decision on granting or refusing a marketing authorisation valid in all Concerned Member States.

The main difference between the MRP and the DP is that the latter is sought in cases where no marketing authorisation has been granted in an EEA country. Under the MRP and DP, manufacturers have greater control over the choice of RMS than with the centralised procedure.

A manufacturer can apply for a **national marketing authorisation** for products not obliged to go through the centralised procedure, if it intends to market a pharmaceutical in only one EEA country, or as a first step in the Mutual Recognition Procedure. Recent legislation to increase transparency requires that national regulatory bodies make marketing authorisations available "without delay" and publicly release clinical documentation, assessment reports and reports on the reasons that underlie the decision. Generic manufacturers often seek approval through national procedures for two reasons: 1) expiry dates of patents and supplementary protection certificates differ from one country to another, and 2) original products may have different forms, strengths, and labelling across countries, necessitating different studies to prove bio-equivalence. Since 2005, however, generic manufacturers have the option of going through the centralised procedure in cases where the original product was approved through the centralised procedure.

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Active ingredient: the chemical substance contained in a *pharmaceutical* which is responsible for its therapeutic effect. Some pharmaceuticals contain more than one active ingredient (combination product).

Active substance: see *active ingredient*.

Anatomic Therapeutic Chemical (ATC) classification system: in this WHO classification system *pharmaceuticals* are divided into different groups according to the organ or system on which they act and/or their chemical, pharmacological and therapeutic properties. The ATC Classification system is divided into five levels. ATC 4 level defines a *therapeutic group*, whereas ATC 5 level defines a single *active ingredient* or a fixed combination of active ingredients. A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses.

Bioequivalent pharmaceuticals: are considered to be bioequivalent if they contain the same molecule (in the same form, dosage type and strength) and are released into, and absorbed by, the body at the same rate. See *generic*.

Brand: the trade or marketing name**.** Brand names used to designate a particular *pharmaceutical* product may differ across countries.

Brand name: see *brand*.

Claw back: a scheme under which *third-party payers* recoup (part of the) *discounts/rebates* granted between various parties to *pharmaceutical* sales transactions, *e.g.* wholesalers and *pharmacists*.

Co-insurance: *cost sharing* in the form of a set proportion of the cost of a service or product.

Compound: see *active ingredient*.

Compulsory license: a license to use a patent, copyright, or other exclusive right that a government forces the holder to grant to others. Compulsory licensing allows generic *manufacturers* to make and sell *generic* versions of *on-patent pharmaceuticals* before patent expiry, in exchange for royalty payments to patent holders.

Co-payment: insured patients' contribution towards the cost of a medical service covered by the insurer. Can be expressed as a percentage of the total cost of the service (also known as co-insurance) or as a fixed amount.

Cost-effectiveness analysis: compares the cost per unit of outcome of alternative therapies with the aim of identifying the most efficient therapy.

Cost sharing: terms of coverage by a *third-party payer* specifying how the patient's share of the costs of health care will be calculated. Cost-sharing mechanisms include

co-payments (known as user fees in tax-financed coverage systems), *deductibles* and co-insurance.

Cross-border trade: the act of importing *pharmaceuticals* into one country (the "import" country) from another (the "export" country) for the purpose of personal consumption in the import country.

Cross-country referencing: see *external price referencing*.

Data exclusivity: protection of an originator pharmaceutical company's data preventing other parties from using these data for a commercial purpose. Concretely, this protection prevents *generic* product *manufacturers* from proceeding to clinical trials and health authorities from evaluating generic product *market authorisation* applications during this period. In the European Union, this period was harmonised to eight years in 2004.

Deductible: patient's share in the form of a fixed amount which must be paid for a service or of total cost incurred over a defined period by a covered person before a *third-party payer* covers all or a percentage of the rest of the cost.

Defined Daily Dose (DDD): the assumed average maintenance dose per day for a *pharmaceutical* used for its main indication in adults.

De-listing: dropping a *pharmaceutical* from a pharmaceutical list (*e.g. positive list*), often resulting in exclusion from *reimbursement*.

Direct-to-consumer advertising (DTCA): the advertising of aimed directly at the public.

Discount: a price reduction granted to specified purchasers of a *pharmaceutical*.

Dispensing fee: payment of the *pharmacist* for the service of dispensing a *pharmaceutical*.

Distributor: a *pharmaceutical* company that sells products it does not produce itself under a licence obtained from the *manufacturer*. Also refers to all actors in the pharmaceutical distribution chain, such as wholesalers or retailers.

Drug: see *pharmaceutical*.

Effectiveness: the extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.

Efficacy: the extent to which an intervention produces a beneficial result under ideal conditions.

Efficiency: a measure of the extent to which health care resources are being used so as to maximisevalue for money.

Evergreening: strategies employed by an originator pharmaceutical company (see *original product*) to extend the patent life of an original product by applying for patents for various attributes of the product on a sequential, rather than simultaneous basis.

Ex-factory price: the *manufacturer's* posted price, in some countries also referred to as list price. Discounts or other incentives offered by *manufacturers* result in an effective price that is lower than the ex-factory price.

External price referencing: the practice of comparing *pharmaceutical* prices across countries. There are various methods applied and different country baskets used.

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Formulary: list of products reimbursed or paid for by a *third-party payer*. See also *open formulary*.

Framework agreement: agreement between social health insurers, national health services or ministries with pharmaceutical *manufacturers* establishing guidelines for policies relating to *pharmaceuticals*. Framework agreements may include provisions relating to *pricing*, promotion, etc. They are used in countries such as France and Spain.

Free pricing: a policy under which *manufacturers* are free to set prices at the level or levels which the market will bear, free from government intervention.

Generic: bioequivalent version of an *original product*. There are branded and *unbranded generics* on the market. Branded generics also have a specific trade name, whereas unbranded generics use the *international non-proprietary name*.

Generic name: see International Non-proprietary Name.

Generic substitution: practice of *pharmacists* substituting a *generic* pharmaceutical, either a branded or *unbranded generic*, for a branded *pharmaceutical*.

Health technology assessment (HTA): the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

Internal reference pricing: a method to compare prices of products in a country with the price of identical (*ATC*-5 level) or similar products (*ATC*-4 level). Often performed in the course of a *reference pricesystem*.

Internal price referencing: see *internal reference pricing*.

International Non-proprietary Name (INN): Identifies *pharmaceutical* substances and *active ingredients*. Each INN is a unique name that is globally recognised and is public property.

International price benchmarking: see *external price referencing*.

List price: see *ex-factory price*.

Manufacturer: a pharmaceutical company that produces *pharmaceuticals* and very often also searches for and develops new drugs. See also *distributor*.

Manufacturer price: see *ex-factory price*.

Market(ing) authorisation: a licence issued by a regulatory agency approving a pharmaceutical for market use based on a determination by authorities that the *pharmaceutical* meets the requirements of quality, safety and efficacy for human use in therapeutic treatment. Also known as a sanitary license.

Me-too: an *original product* that is approved subsequent to another product that is comparable or similar in composition and in therapeutic effect to the me-too product.

Medicinal product: see *pharmaceutical*.

Medicine: see *pharmaceutical*.

Negative list: list of *pharmaceuticals* not covered by a *third-party payer* (see also *positive list*).

New chemical entity (NCE): a drug approved for *marketing authorisation* with an *active ingredient* not present in any drug previously approved by a regulatory agency.

New molecular entity (NME): see *new chemical entity*.

Non-prescription medicine: see *over-the-counter pharmaceutical*.

Off-patent pharmaceutical: *original product* whose patent has expired.

Off-patent product: see *off-patent pharmaceutical*.

On-patent pharmaceutical: an *original product* whose patent is still in force.

Open formulary: a *pharmaceutical* benefit design that provides coverage for drugs on the *formulary* (if any) as well as other drugs not specifically listed.

Original preparation: see *original product*.

Original product: the first version of a *pharmaceutical*, developed and patented by an originator pharmaceutical company which receives exclusive rights to market the product for a specified period of time. An original product has one or more trade names used for marketing purposes, its so-called *brand* names.

Original substitution: see *generic substitution*.

Orphan drug: a *pharmaceutical* which only has a limited target population or which treats a rare disease thus limiting its commercial and financial potential.

Out-of-pocket payments: payments made by a health-care consumer that are not reimbursed by a *third-party payer*. This includes all forms of *co-payments*, co-insurance and deductibles as well as payments for non-covered services and informal payments for health-care services.

Over-the-counter pharmaceutical (OTC): *pharmaceuticals* which may be dispensed without a doctor's prescription being submitted and which are in some countries available via self-service in pharmacies and/or other retail outlets (*e.g.* drug stores, supermarkets).

Parallel import: see *parallel trade*.

Parallel trade: the act of importing *pharmaceuticals* into one country (the "import" country) from another (the "export" country) and placing them on the market outside the formal channels authorised by the product's *manufacturer* or licensed distributors.

Pharmaceutical: any *active ingredient* or a combination of two or more active ingredients in a product which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a pharmaceutical.

Positive list: see *formulary*.

Pharmaceutical form: the pharmaceutical-technological form in which an *active substance* is made available. *Pharmaceuticals* may be administered in solid form (*e.g.* tablets, powders), in semi-liquid form (*e.g.* ointments, pastes), in liquid form (*e.g.* drops, injectables, infusions) or in gaseous form (inhalation).

Pharmaco-economics: see *pharmaco-economic evaluation*.

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Pharmaco-economic evaluation: assessment of the relationship between costs and outcomes for a given product, and, possibly, comparisons to costs and outcomes of alternative treatments, pharmaceutical or not.

Pharmacist: a person trained and licensed to prepare and distribute medicines and to give information about them.

Pharmacy margin: the gross profit of pharmacies expressed as a percentage of the *retail price*.

Pharmacy mark-up: the gross profit of pharmacies expressed as a percentage of the *pharmacy purchasing price*.

Pharmacy purchasing price: the price charged by wholesalers to the retailers (usually pharmacies). It includes any *wholesale mark-up*.

Positive list: see *formulary*.

Preferred drug list (PDL): a term sometimes used as an alternative to *formulary*, but more precisely refers to a list of preferred medicines within selected drug classes on a formulary for which a patient's co-payment is lower and/or prior authorisation is not required.

Prescribing budget: the maximum amount of money to be spent on *pharmaceuticals* in a specific region or for an individual physician or a group of physicians, for a specified period of time, fixed ex-ante. Prescribing budgets are a cost-containment measure used by *third-party payers*.

Prescription Fee/Charge: a set amount to be paid by a patient for each item prescribed by a physician and dispensed at the expense of a *third-party payer*, *i.e.* a form of fixed *co-payment*.

Prescription-only-medicines (POM): *pharmaceuticals* that may be dispensed only on a doctor's prescription.

Price-volume agreement: the price of a pharmaceutical is agreed to between a *third-party payer* and a pharmaceutical *manufacturer* based on a forecasted volume of sales. If the actual sales volume exceeds the forecast, the price of the *pharmaceutical* may be revised downwards or the manufacturer asked to pay a *rebate*.

Pricing: the act of setting a price for a *pharmaceutical*.

Pricing policy: plan or course of actions used by government authorities, or *third-party payers,* to influence the amount paid by purchasers or the amount received by sellers (*e.g. free pricing*, regulated pricing – see *regulated price*).

Prior authorisation: formal agreement from a *third-party payer* for the *reimbursement* of a treatment, prior to the purchase of the treatment.

Procurement: the act of purchasing a *pharmaceutical* by a public authority.

Product life-cycle management: refers to a range of practices used by *manufacturers* of *originalproducts*, including but not limited to patent-related strategies, intended to limit or delay competition by *generics*.

Rebate: a partial refund following a purchase.

Reference price: a maximum *reimbursed amount* set by a *third-party payer* for a defined group of *pharmaceuticals* judged to be similar. Usually, one reference price is set for all products in a given *ATC*-4 and/or *ATC*-5 level group. See *reference price system*.

Reference price system: a scheme used by *third-party payers* to set a common *reimbursement price* for a defined group of *pharmaceuticals* judged to be similar. Patients buying a pharmaceutical that is part of a group for which a *reference price* has been set must pay the difference between that price and the *retail price* of the pharmaceutical in question, in addition to any fixed or percentage *co-payments*.

Registration: see *market(ing) authorisation*.

Reimbursement: the share of costs (for a service or a *pharmaceutical*) which the *third-party payer* pays. One-hundred per cent reimbursement means that the third-party payer accepts 100% of the costs for a *pharmaceutical* or healthcare service.

Reimbursed amount: the actual sum paid by a *third-party payer* to an insured person or seller of a *pharmaceutical*. May be equivalent to the full *reimbursement price* (as in Austria) or set as a percentage share of the reimbursement price (as in Denmark).

Reimbursement level: the share of total charges for a service or a *pharmaceutical* which the *third-party payer* pays. For example, an 80% *reimbursement level* means that the third-party payer assumes 80% of the costs for a pharmaceutical or healthcare service.

Reimbursement price: the basis for *reimbursement* of pharmaceuticals in a health care system, *i.e.* the maximum amount that a *third-party payer* will pay for a particular *pharmaceutical*. See *reimbursed amount*.

Retail price: the price charged by retail *pharmacists* or other retailers to the general public.

Switch: reclassification of the dispensing status of a *pharmaceutical* from *prescription-only* to *over-the-counter*.

Supplementary Protection Certificate (SPC): gives originators (see *original product*) a complementary period of market exclusivity beyond patent expiry to compensate for delays of marketing in the *pharmaceutical* sector. SPCs are available in EU countries. Similar protection exists in other countries.

Therapeutic group: *pharmaceuticals* from the same pharmacological class, such as statins.

Therapeutic referencing: see *internal reference pricing*.

Third-party payer: any entity, public or private, that pays or insures health or medical expenses on behalf of beneficiaries or recipients of the coverage.

Unbranded generic: see *generic*.

Value-added tax (VAT): a tax levied on the sale of goods and services (compulsory for EU Member States). The VAT rate for pharmaceuticals in the EU is often lower than the standard minimum VAT-rate of 15%.

Wholesale margin: gross profit of wholesalers, expressed as a percentage of the *pharmacy purchasing price*.

Wholesale mark-up: gross profit of wholesalers, expressed as a percentage of the *ex-factory price*.

Wholesale price: see pharmacy purchasing price.

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Various sources were used to compile this glossary. The following sources were consulted most frequently or were used to extract a verbatim definition:

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WHO Collaborating Centre for Drug Statistics Methodology, *www.whocc.no/atcddd/*.

List of Abbreviations

ADR	Adverse Drug Reactions
AMP	Average Manufacturer Price
ANAFAM	Asociación Nacional de Fabricantes de Medicamentos
ASMR	Amélioration du Service Médical Rendu
ATC	Anatomic Therapeutic Chemical Classification
BP	Best Price
BPAs	Blanket Purchase Agreements
CBO	Congressional Budget Office
CBS	Centraal Bureau voor de Statistiek (Netherlands)
CEPS	Economic Committee for Health Products
CME	Continuing Medical Education
CP	Centralised Procedure
DALY	Disability Adjusted Life Year
DDD	Defined Daily Dose
DoH	Department of Health
DP	Drugs Payment
DP	Decentralised Procedure
DRA	Deficit Reduction Act
DRG	Diagnostic-Related Group
DTC	Drug and Therapeutic Committees
DTCA	Direct-to-Consumer Advertising
DTI	Department of Trade and Industry
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industry Associations
EGA	European Generics Manufacturers Association
EMEA	European Medicines Evaluation Agency
EPC	European Patent Convention Treaty
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
FTC	Federal Trade Commission
GAO	General Accounting Office
GDP	Gross Domestic Product
GP	General Practitioner
HD	Health Data
IOM	Institute of Medicine
IPR	Intellectual Property Rights

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LFN	Sweden's Pharmaceutical Pricing Agency
LOOP	Law of One Price
LTI	Long Term Illness
MAGR	Mean Annual Growth Rate
MCC	Marginal Cost of Capital
MPA	Medical Products Agency
MRP	Mutual Recognition Procedure
MRR	Marginal Rate of Return
NAS	New Active Substances
NCE	New Chemical Entities
NCU	National Currency Unit
NHS	National Health Services
NICE	National Institute of Clinical Excellence
NME	New Molecular Entities
ÖBIG	Austrian Health Institute
OOP	Out-of-pocket
OTC	Over-the-counter (non-prescription) drugs
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Pharmaceutical Benefits Management
PDL	Preferred Drug List
PDP	Prescription Drug Plan
PICTF	Pharmaceutical Industry and Competitiveness Task Force
PMPRB	Prescription Medicine Prices Review Board
POM	Prescription-only medicine
PPP	Purchasing Power Parity
PPRI	Pharmaceutical Pricing and Reimbursement Information
PPRS	Pharmaceutical Price Regulation Scheme
R&D	Research and Development
RBP	Rémunération basée sur les prestations
ROI	Return on Investment
SKK	Slovak koruna
SPC	Supplementary Protection Certificate
TRIPS	Trade-Related Aspects of Property Rights
USC	Uniform System of Classification
USP	US Phamacopeia
VA	Veterans Affairs
VAT	Value Added Tax
VFA	Verband Forschender Arzneimittelhersteller e.V.
VHA	Veterans Health Administration
VISN	Veteran Integrated Service Network

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