

**Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies**

**Priority Medicines for Europe and the World  
"A Public Health Approach to Innovation"**

**Update on 2004 Background Paper**

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**Background Paper 8.3  
Pricing and Reimbursement Policies:  
Impacts on Innovation**

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### 1. Introduction

In recent years, many industrialized countries have been confronted with rising healthcare expenditures. As increases in healthcare expenditures commonly exceed a country's economic growth, governments have turned to various policies aimed at controlling both healthcare and pharmaceutical expenditure.<sup>1,2</sup> During the last decade, European countries - particularly those countries hit by the global financial crisis - have implemented a range of cost-containment measures in the pharmaceutical sector.<sup>1,3</sup> Governments have both an obligation to improve public health (through facilitating access to needed therapies for its citizens), a need to control healthcare expenditures - as a substantial part of healthcare expenditures are financed publicly - and commonly seek to reward pharmaceutical innovation. These goals are potentially conflicting and therefore, policy decisions may well require trade-offs across competing policy objectives.<sup>2</sup>

The current focus on cost containment measures has given rise to concerns regarding the sustainability of pharmaceutical innovation. Pharmaceutical companies earn back investments in pharmaceutical R&D through profits generated by the prices of a minority of products that make it from the discovery phase onto the market, as new medicines entering the market will experience a period of market exclusivity due to patent protection. If pharmaceutical prices are not sufficient to (i) earn back investments and (ii) generate resources that can be reinvested in the development of new medicines, price controls and stringent reimbursement regulations have the potential to negatively impact pharmaceutical innovation<sup>1,2,4,5,6</sup> as for the manufacturer of an innovative medicine, coverage and reimbursement are the key to economic success that is essential for sustaining its R&D.<sup>7</sup>

In the context of Priority Medicines, therefore, appropriate policies and incentives for R&D - that are partly generated by pricing and reimbursement policies - are an important instrument to address pharmacotherapeutic gaps. The objective of this background paper is to discuss current pricing and reimbursement policies that may be able to align conflicting policy objectives - cost containment, access to medicines, rewarding innovation - and to identify priorities for research based on this discussion. Different sources have been used, including scientific publications, grey literature, interviews with experts, and policy documents for writing this paper.

The 2004 Priority Medicines Report included a background paper on the "Approach to the Valuation and Pricing of Future Medicines" which particularly looked for approaches for low- and middle-income countries and proposed differential pricing as a possible way forward. The focus of this background paper is broader, as the impact of current pricing and reimbursement practices in Europe on pharmaceutical innovation will be discussed. In this report, new developments are presented with regard to value assessments, pricing and reimbursement policies, processes and initiatives, and evidence about existing practices on whether they are able to enhance innovation will be assessed. The focus of this background paper will be on Europe. However, developments in the "rest of the world", both other high-income and middle- and low-income countries will be considered as well.

This background paper discusses three main themes: the first part of this paper discusses how value and innovation are determined in the context of European countries, and analyses how system and policy features could contribute to aligning different policy objectives. The

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second theme of this paper addresses how price and volume are managed in European countries. In the third part of this paper the different networks and infrastructures in Europe are discussed, including the way in which they could contribute to enhancing innovation. In the conclusion of this paper, a number of research priorities are identified that could enhance our knowledge of pricing and reimbursement policies and the way they could impact innovation.

The paper contains a number of annexes that show price data of selected medicines and give an overview of high level initiatives by the European Commission.

## 2. The (added) value of innovation

This section of the background paper starts with a brief assessment of how innovation and value are currently assessed in European pricing and reimbursement systems. In order to develop ways in which the (added) value of innovative medicines is rewarded, while simultaneously adhering to goals of access and sustainability of publicly funded healthcare systems, it needs to be determined *how* and *what type of* innovation should be rewarded. Subsequently, the reimbursement of medicines in Europe is discussed, with a focus on Health Technology Assessment (HTA) and economic evaluations as they are increasingly being used in reimbursement decision-making. This report discusses both how decision-making about the reimbursement of medicines currently is performed by countries, as well as how systems could be improved to achieve policy goals. HTA and economic evaluation are considered important tools because of their ability to govern efficient use of resources while rewarding pharmaceutical innovation. However, unlocking the value of these tools requires that several conditions to be met, these are discussed in this section. Finally, a number of topics related to the reimbursement of medicines are discussed, such as delays in access, orphan medicines, limited budgets, and stratified medicines, that all pose a challenge to current reimbursement systems in European countries. Although pricing of medicines and reimbursement of medicines are closely interlinked in decision-making, specific *pricing* policies are discussed separately in the next section on managing price and volume.

### 2.1 Innovation and value

#### 2.1.1 Pharmaceutical R&D

Regardless of major scientific advances in pharmaceutical research over the last 60 years, a decline in pharmaceutical R&D efficiency has been observed<sup>8</sup> while the costs of R&D have risen exponentially.<sup>9</sup> This phenomenon has been referred to as Eroom's Law: the number of new medicines approved by the FDA in the United States per billion US dollars spent on R&D has halved every nine years.<sup>8</sup> Even though Eroom's law refers to the United States market, empirical evidence suggests that there are no significant differences between European and United States R&D productivity.<sup>10</sup> Therefore, this so-called 'productivity crisis' might have relevant impacts on the European pharmaceutical market as well. In short, this means that although the number of medicines entering the market is not increasing, they are becoming more costly to develop. It has been estimated that the costs of bringing a single

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medicine to the market have increased from €149 million in 1975 to €868 million in 2000.<sup>11</sup> Although the methods for such calculations have been criticized<sup>12</sup> the costs of developing and bringing medicines to the market have increased. The high level of uncertainty of the R&D process is a main reason for high R&D costs: only a very low percentage of all molecules that enter the discovery phase will eventually reach the market,<sup>13</sup> and out of all pharmaceuticals that do reach the market, only a minority will subsequently recover the investment costs.<sup>11</sup> (See the Background Paper 3 for a more in-depth discussion on drug development). Therefore, it is generally accepted that the price a medicine that is covered by public payers should reflect a sufficient compensation for R&D investment, in order to provide companies with an incentive to continue the development of innovative medicines. What exactly constitutes 'sufficient compensation' for R&D, and whether each country should contribute equally to R&D (see Section 3.1.5 on differential pricing), is heavily debated.

### 2.1.2. Innovative medicines

Medicines that reach the market can be classified in many different ways: by patent status (patented medicine or generic medicine), indication (high volume indications, orphan indication, or stratified medicine), or by molecular structure (first-in-class or me-too). Different policies might be needed for different types of medicines, and policy aims might vary for different types of medicines as well. Throughout this background paper, the effects and challenges of policies according to the type of medicine will be distinguished, and the following classification of medicines has been used: first, it is recognized that patented medicines require different pricing and reimbursement policies than off-patent medicines (generics). Generic medicines are discussed separately in this section. For patented medicines, medicines with added therapeutic value and medicines without added therapeutic value are distinguished between. 'Added therapeutic value' is defined below. Furthermore, it is recognized that policy makers tailor policies to deal with high volume medicines and low volume (but high cost) medicines (orphan medicines and stratified medicines). The 'ideal' reimbursement policy, therefore, is one that sufficiently rewards innovation while securing value for money for the healthcare system and ensuring equitable and timely access to medicines.<sup>4,14</sup>

A common definition of what constitutes an 'innovative medicine' is currently lacking. Furthermore, countries use different definitions of the type of innovation that is considered worthy of rewarding. From a public health perspective, however, the level of innovativeness of a medicine is primarily defined by the benefits the medicine generates for patients. These benefits can be in the therapeutic or clinical domain, the quality of life domain, but also in the socio-economic domain.<sup>4</sup> Examples of benefits in the socio-economic domain include a medicine that would prevent (expensive) hospital admissions or that would enable patients to work.

An OECD study assessed the innovative value (as defined by either a new chemical structure, a therapeutic improvement, or both) of all new chemical entities (NCEs) launched during 1972-2002. They found that 10% of all NCEs launched during this period were considered a 'radical innovation', which was defined as a new chemical structure combined with a therapeutic improvement.<sup>2</sup> Most medicines that reach the market therefore do not result in a dramatic therapeutic improvement over existing treatments and would be considered 'incremental innovations'. Notwithstanding, a first-in-class medicine is not

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always the best-in-class medicine<sup>15</sup> and it is difficult to predict, before the end of large confirmatory trials at the end of clinical development, whether a medicine actually generates a substantial therapeutic improvement or not. Furthermore, the value of a medicine can change over time and could both decrease (once more medicines are approved for the same indication), or increase over time. A pricing and reimbursement system that is not adapted to deal with different types of medicines therefore may not result in the optimal stimulation of innovative R&D.<sup>15</sup>

Once a medicine's period of market exclusivity ends, generic competitors will be able to enter the market, which may result in fierce price competition. Although the role of policies regarding generics are not aimed at rewarding innovation (and they are discussed in Section III in more detail), generics are relevant in the context of rewarding innovation through pricing and reimbursement as a combination efficient generics policies could offer the (public) pharmaceutical bill a substantial savings potential – which would free up resources that could be allocated to financing new and expensive medicines. A high generic penetration and low generic prices should be the aim of efficient generics policies.

### **Innovation and value: research priorities**

- Study the different definitions of innovation and how they play a role in the reimbursement process. A shared understanding of value – in the context of reimbursement systems for medicines – is currently lacking. Definitions of value and innovation that are currently used by countries should be assessed, in order to provide a clear picture of innovation and value of medicines in the reimbursement systems of European countries.
- Assess to what extent reimbursement systems of European countries explicitly offer rewards for innovation, and whether this is subsequently reflected in decision making.

## **2.2 Decision-making in reimbursement**

### **2.2.1 Reimbursement of medicines**

Governments generally consider the following questions in determining whether or not to make healthcare technologies available: does it work, does it add value to society, it is a reasonable cost to the public, and is it the best way to deliver the service? In decision-making processes regarding the reimbursement of medicines, it needs to be established whether a medicine should be considered as eligible for reimbursement. Subsequently, if the medicine is indeed classified as 'reimbursable', it needs to be assessed how much of the price the public payer should (or is able to) cover. The process of setting a price (pricing) and deciding on the level of coverage by public payers (reimbursement) therefore are strongly interlinked. The assessment process usually includes criteria such as efficacy, effectiveness, safety, ease of use, and added therapeutic value, beside cost-effectiveness.<sup>16</sup>

It has been argued that national reimbursement systems should adhere to 'accountability for reasonableness', which means that four conditions need to be met<sup>17</sup>: (i) decisions need to be publicly accessible, (ii) the rationale for coverage decisions should reflect acceptable and relevant principles (reasonable), (iii) there is a procedure for challenging and disputing decisions, and (iv) there is regulation to ensure these conditions are met. These terms are



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incorporated in the EU Transparency Directive<sup>18</sup> as well. Designing a pharmaceutical pricing and reimbursement policy is a competence of EU Member States, although they have to comply with the EU Transparency Directive (e.g. time-lines, justification of reason for their decision).

Several European countries share the implicit or explicit health policy objectives of sustainability, equity, and quality of care, but the way in which these are handled can differ substantially between countries.<sup>16</sup> Furthermore, most countries also have additional non-health objectives - such as rewarding innovation and investments in R&D - although systems are not very clear about the actual role of such objectives.<sup>16</sup> European countries use a variety of policies for reimbursement decisions. All countries have either a positive or negative list that specifies which medicines are publicly covered (positive list) or are excluded from public coverage (negative list). A number of countries use internal price referencing to determine the maximum reimbursable price for a group of new medicines that have therapeutic alternatives. Furthermore, several countries use Health Technology Assessment (HTA) to determine whether a medicine should be reimbursed or not.<sup>1,19</sup> Although HTA can be used for all new medicines entering the market, many countries use HTA procedures for a subset of medicines only, where medicines are commonly differentiated according to the existence of therapeutic alternatives or whether they have added therapeutic value.

Pricing and reimbursement policies also include external price referencing (international price benchmarking); internal reference pricing; decision making based on Health Technology Assessment (HTA) and economic evaluations; value-based pricing; caps and copayments; taxes; price-volume agreements; fixed margins in distribution channels; and tendering. The impact of these policies on the price of medicines, the availability of and access to medicines, and pharmaceutical expenditure vary.

### 2.2.2 HTA and economic evaluation

European countries that currently use HTA in reimbursement decision-making are Belgium, Denmark, Sweden, the Netherlands, Finland, the United Kingdom, Ireland, Portugal, Norway, Estonia, Latvia, Lithuania, Germany, Hungary and Poland, and several other countries are planning the implementation of HTA as a reimbursement tool as well.<sup>1</sup> HTA is a generic term, and each country applies HTA in its own way. Notwithstanding, the European Network for HTA (EUnetHTA) defines HTA as a multidisciplinary process in which medical, social, economic, and ethical issues related to the use of a health technology are assessed in a systematic, transparent, unbiased, and robust manner.<sup>20,21</sup> Often, an economic evaluation is part of HTA, but HTA incorporates more factors in decision making than only economic factors. It is therefore important to note that 'decision-making using HTA' does not *necessarily* involve the use of economic evaluations, as the foundation of HTA is scientific evidence of patient outcomes from health interventions<sup>22</sup>, meaning that the relative efficacy or effectiveness of a medicine is the central element of the assessment. Often, however, HTA includes some financial or budget evaluation, albeit not always a full economic evaluation.

### Box 8.3.1: Measuring costs and effects in economic evaluations

#### Costs

The costs that are included in an economic evaluation depend on the perspective that is taken – usually, either a healthcare perspective or a societal perspective. With a healthcare perspective, all costs related to healthcare consumption (i.e. direct costs) are taken into account. This means that not just the costs of the pharmaceutical are included in the analysis, but also the costs of, for example, hospital stay. If a new medicine prevents patients from being admitted to the hospital as compared to an existing treatment, this could result in lower total costs of the new treatment, even if the new treatment would be priced higher than the existing treatment. When a societal perspective is taken, not only costs of healthcare consumption are included in the assessment but indirect costs are taken into account as well. Indirect costs comprise of costs that fall outside the scope of healthcare but are caused by the disease and include travel costs (to healthcare providers), productivity costs (not being able to work) and the costs of informal caregivers (who dedicate their time to caring for the patient). The societal perspective considers the costs of disease to society (lost productivity, informal care costs) as well as healthcare-related costs, whereas the healthcare perspective does not consider indirect costs. The perspective taken in an economic evaluation usually is guided by who is performing the analysis: to a health insurer, the healthcare perspective might be more informative for decision-making than to a government agency that does need to take societal costs into account.

#### Health effects

Health effects in an economic evaluation can be measured in different ways (life years gained, hospital admissions avoided, deaths prevented) but a commonly used health effect measure is the quality-adjusted life year (QALY). A QALY combines the length of life lived with the health-related quality of life in which life is lived – where 1 represents perfect health and 0 represents death. One QALY therefore can be interpreted as one year of life lived in perfect health. The QALY is a generic health measure as it can be used to assess the impact on a patient's health, regardless of the treatment or the patient's disease. Therefore, assessing the value of a medicine for any given indication can be determined using the same measure, making it a practical and widely applicable measure of health.

An economic evaluation is an assessment of the relative merit or value of health services, in which two main questions are asked: first, is this health procedure, service, or program worth doing compared with other things that could be done with the same resources, and second, is there satisfaction that the health care resources (required to make the procedure, service, or program available to those who could benefit from it) should be spent in this way rather than in some other way?<sup>23</sup> An economic evaluation therefore always involves a comparative analysis of alternative courses of action.<sup>23</sup> There are four types of economic evaluation: *cost-minimization analysis*, in which the costs of two or more treatments are assessed (when the effectiveness of two treatments is assumed to be equal), *cost-effectiveness analysis*, in which both health effects as costs of two or more treatments are assessed, *cost-utility analysis*, in which both health effects and costs of two or more treatments are assessed and in which the health effects are expressed as quality-adjusted life years (QALYs) (see box

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8.3.1), and *cost-benefit analysis*, in which both health effects and costs are expressed in monetary terms – where the health effects are expressed in the willingness to pay to achieve those health effects.<sup>23</sup> The term cost-effectiveness analysis is commonly also used for studies that are in fact a cost-utility analysis. Pharmacoeconomics is a term that is used for the economic comparison of two or more medicines, which is usually done through an economic evaluation.

In a cost-effectiveness analysis, the costs ( $C$ ) and health effects ( $E$ ) of a new treatment are compared against the costs and health effects of an existing treatment.<sup>24</sup> Consequently, the incremental costs and effects are expressed in an incremental cost-effectiveness ratio (ICER) that is calculated by the following formula:  $ICER = \Delta C / \Delta E$ . An ICER therefore expresses the amount of resources that will be required to gain one unit of health (which is one QALY in a cost-utility analysis), if the existing treatment would be replaced by the new treatment.<sup>23</sup>

### 2.3 HTA and decision-making in the reimbursement of medicines: challenges

#### 2.3.1 Willingness to pay

When methods and procedures for the assessment of the value of medicines, such as the use of economic evaluations, are properly and consistently applied in decision-making, this is likely to result in a more efficient allocation of resources. In such a system, only medicines that offer value for money to society will be reimbursed, however ‘value’ would be defined by society. When the cost-effectiveness of medicines is considered, this implies that only medicines that are priced at or below the maximum that society will be willing to pay for the added value will be reimbursed. In such a case, the system would result in *static* efficiency which means that the allocation of resources is efficient (i.e. cost-effective). However, there is no guarantee that such a system will result in *dynamic* efficiency as well. Dynamic efficiency means that the system also creates sufficient rewards for future innovation, and can only be achieved if medicines are priced such that they sufficiently reward innovation, offering both returns on past investments as well as providing the resources and incentives for future investments. It has been noted by others that in the context of creating incentives for the development of priority medicines, a more dynamic perspective on cost-effectiveness may actually help to stimulate R&D as it would create the financial incentives for indications where therapeutic gaps exist.<sup>25</sup> Therefore, even though the use of economic evaluations in reimbursement decisions would be a required step towards aligning policy goals of cost-containment, access to medicines, and rewarding innovation, the use of economic evaluations in itself does not guarantee that long-term effects of rewarding innovation are reached as well. In order to achieve dynamic efficiency, systems need to ensure that the rewards that are offered through financing of medicines are sufficient. A major component of dynamic efficiency therefore is the maximum willingness to pay for added value.

Several countries assess the added value of medicines through determining the incremental cost-effectiveness of a medicine, as measured by the incremental costs per QALY. Once the incremental costs per QALY gained of a medicine are assessed, it needs to be determined whether or not the incremental costs per QALY gained offer value for money to society (appraisal). Most countries that use economic evaluations in decision-making do not use explicit thresholds for the maximum costs per incremental QALY gained they are willing to pay, with a notable exception being the United Kingdom. However, even in countries where

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no explicit thresholds are used, willingness to pay is implicit through historical reimbursement and coverage decisions<sup>24</sup> given that there is some degree of consistency in decision-making.<sup>26</sup> These signals are an important consideration in a firm's R&D portfolio management strategy as a company can integrate a willingness to pay threshold in its net-present value (NPV) calculations during product development.<sup>24</sup> Furthermore, both thresholds that are either too low or too high will result in economic inefficiencies - and can reduce societal welfare.<sup>24</sup> Therefore, a country's willingness to pay is one of the most relevant for a payer who wants to reward innovation through financing the added value of medicines.

The lack of a reimbursement threshold could weaken decision-making based on economic evaluations as without a threshold, the decision maker itself cannot know against which scale the cost-effectiveness of a pharmaceutical should be measured.<sup>1</sup> Yet the only European country that so far has made explicit statements about their willingness to pay per QALY is the United Kingdom, in which a range of £20 000 - £30 000 per QALY gained is used. Many have claimed that the United Kingdom is an exception in its explicit statement about its thresholds due to the nature of its healthcare system, which is financed through taxes and has regional budget holders which make the actual budget impact of new treatments much more visible. Although this may play a role, it does not mean that other national payers do not *need* a willingness to pay threshold. Still, payers in most countries remain reluctant to be more explicit about maximum thresholds.<sup>27</sup> This comes at a risk, however, as it may increase prices: when a payer determines whether a medicine's incremental cost-effectiveness ratio is acceptable or not acceptable on a case-by-case basis, companies may ask for whatever price they think the market will bear.

However, there are understandable reasons for policy makers' reluctance about setting explicit willingness to pay thresholds. Setting explicit thresholds would invoke public debate regarding societal willingness to pay and could be criticized for decision-making based on 'numbers alone' (although other considerations still can play a role even when an explicit threshold is set, the so-called 'soft' threshold).<sup>26</sup> Furthermore, for policy makers, not setting an explicit threshold allows for arbitrariness, flexibility, and ad-hoc considerations.<sup>26</sup> It has been argued that, in spite of policy makers' reluctance to set explicit thresholds, a move towards more explicit thresholds can be expected in the future based on the 'law of unintended consequences': decision making based on cost-effectiveness evidence will enable retrospective analysis of these decisions, which could provide stakeholders with the opportunity to assess the (in)consistency of the decision-making process.<sup>26</sup> Even though setting explicit thresholds is a politically sensitive issue, not doing so comes at a risk – including a lower transparency and a lower consistency, and therefore predictability, of the decision-making process.<sup>26</sup>

### 2.3.2 Moving towards the use of economic evaluations in reimbursement

When a country is planning to implement the use of economic evaluations and cost-effectiveness evidence in reimbursement decision-making, this will require technical capacities that take time to develop.<sup>28</sup> Furthermore, small countries that lack the means and/or market size to effectively implement such policies may find it challenging to implement extensive reimbursement policies and procedures. For such countries, collaborative efforts with other (small) countries could help in this matter. International collaborations and networks are discussed in Section IV of the background paper. When a

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country is seeking an efficient allocation of resources, all new medicines entering the market would have to be assessed for their cost-effectiveness (as is the case in the Swedish system). In practice, however, it is expensive and time-consuming to assess every new medicine. In most countries, therefore it is only required to submit cost-effectiveness evidence for a subset of medicines, and medicines for which a cost-effectiveness analysis needs to be performed are usually high cost medicines or medicines claiming added therapeutic value. Although Sweden requires an economic evaluation for every medicine seeking reimbursement, the option is available to only provide comparative cost data (i.e. a cost minimization analysis) when the medicine is not better in improving health outcomes than comparators, in response to this particular issue.<sup>29</sup> (see also Box 8.3.2). Other countries could consider such options as well.

### HTA, reimbursement of medicines, willingness to pay: Research priorities

- Assess to what extent reimbursement systems throughout Europe are consistent in their willingness to pay for innovation, and what the reasons for discrepancies are.
- Study why decision-makers do or do not use explicit thresholds.
- It should be studied whether there are possibilities for joint efforts between countries for areas of unmet medical needs for setting thresholds for willingness to pay.

### 2.3.3 Methodology development

HTA has expanded enormously since its conception 35 years ago – in terms of its analytical techniques as well as its importance in priority setting and decision making.<sup>22</sup> As more and more European countries move towards the use of HTA and economic evaluation in coverage decisions, policy makers are faced with a number of challenges. Countries do not always have the resources to perform an HTA assessment, which means that policy makers frequently will have to rely on studies that have been performed in other settings.<sup>30</sup> The data requirements for economic evaluation differ between countries as many payers have their own guidelines for economic evaluations.<sup>31</sup> Given the lack of available, local data, it is important that methods used are comparable and that results are reported in such a way that the generalizability and transferability of a study's results can be assessed.<sup>30</sup>

#### Box 8.3.2: Reimbursement in Sweden

Sweden's current reimbursement system was introduced in October 2002. Reimbursement and pricing processes are completely integrated in Sweden and the national competent authority (the Dental and Pharmaceutical Benefits Board (TLV)) will communicate a joint reimbursement and pricing decision. The eligibility criteria for reimbursement, as laid down in the Act on Pharmaceutical Benefits, can be summarized mainly by three principles:

**The human value principle** underlines the respect for equality of all human beings and the integrity of every individual. Therefore it is not allowed to discriminate against people because of sex, race, age, or other characteristics when making reimbursement decisions.

**The need and solidarity principle** states that those in greatest need have priority in the

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reimbursement of medicines. People with more severe diseases therefore are prioritized over people with less severe conditions. According to TLV, one example of how the need and solidarity principle has been put into practice was TLV's decision to withdraw the reimbursement for the H2 antagonists within its review of medicines against diseases caused by stomach acid. TLV concluded that H2 antagonists could be a cost-effective choice for some milder symptoms like heartburn, but that these diseases result in such small losses in quality of life that the treatment should not be reimbursed by society. Instead, the patients should bear the full cost of using these pharmaceuticals. In this case the need and solidarity principle took precedence over the cost-effectiveness principle.

**The cost-effectiveness principle** states that the cost for using a medicine should be reasonable from a *medical, humanitarian, and social-economic* perspective. This means that Sweden uses a societal perspective, in which both direct as indirect costs are included in the analysis. Benefits that are considered are two-fold: effects on health, e.g. a longer life expectancy or a higher health-related quality of life and cost savings are both considered.

A pharmaceutical company is required to demonstrate the cost-effectiveness of a new (originator) medicine by submitting a pharmacoeconomic analysis to TLV. Guidelines state that the analysis should be performed from a societal perspective, the treatment in question should be compared with the most appropriate alternative treatment in Sweden, the analysis should include the whole patient population to which the reimbursement application refers, all relevant costs associated with treatment and illness should be identified, quantified and evaluated, and the time-frame for the study shall cover the period when the main health-effects and costs arise. Furthermore, a cost-effectiveness analysis, with quality-adjusted life years (QALYs) as outcome measure is recommended and for treatments that mostly affect survival, both QALYs and life years gained should be shown. If surrogate end-points are used, the account should also include modeling from these end-points to illustrate the effects on morbidity and mortality, i.e. QALYs gained. If it is difficult to use QALYs (e.g. with severe pain for a short time in connection with treatment), then a cost-benefit analysis with willingness to pay may be used as a measure of effect. Finally, if there is supporting evidence that the medicine in question has the same health effects as the best comparable treatment, a cost comparison may suffice.

In conclusion, the Swedish system is a valued-based pricing system, in which the added value is assessed for all new medicines and where higher prices are granted to medicines that demonstrate higher added value – where added value can consist of both increased health effects or costs savings – either within the healthcare sector as well or cost savings to society.

Source: Redman, T., Köping Höggård, M. PPRI Pharma Profile Sweden 2007. Vienna: Pharmaceutical Pricing and Reimbursement Information (PPRI); 2007. Via [http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/Sweden\\_PPRI\\_2007.pdf](http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/Sweden_PPRI_2007.pdf)<sup>29</sup>

Economic evaluations are considered *generalizable* when the results can be applied to another setting (e.g. another country) without any needed adjustment, whereas an economic evaluation is *transferable* if its results can be adapted to apply to another setting.<sup>31</sup> A wide variety of factors can influence the generalizability and transferability of study results, but the main factors are the baseline risk, the treatment effect, health utilities, resource use, and unit costs.<sup>31</sup> An assessment of 27 different sets of guidelines for cost-effectiveness studies

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found that in general, estimates of treatment effect are considered more transferable whereas economic factors are less often considered transferable.<sup>31</sup> Interestingly, it was found that countries with limited financial and human resources for conducting separate local studies were more flexible with regard to generalizability of economic evaluations.<sup>31</sup> Furthermore, it was found that despite the existence of guidelines, considerable variation in applied methods continues to exist, even between studies conducted for the same jurisdiction.<sup>30</sup>

Even though economic evaluations are not directly generalizable, measures can be taken to improve the transferability of economic evaluations from one setting to another. Such measures could greatly increase the value from the investment in economic evaluations and could especially benefit small countries that lack the resources to conduct economic evaluations.<sup>32</sup> In order to improve the transferability of economic evaluations, it is recommended that study sites are selected such that the sites are representative of the jurisdiction for which economic data are collected, patients are selected such that they reflect normal a clinical caseload, the comparator that is 'current practice' is included in the study, data should be collected to enable an analysis from different cost perspectives, resource data apart from cost data should be collected, and health-related quality of life should be measured to enable for inserting region-specific valuations for health states.<sup>32</sup>

The EUnetHTA is currently working on the development of tools for international HTA – and it is planned that joint assessments will be carried out in a pilot phase.<sup>33</sup> EUnetHTA however, does not consider costs – it is developing tools to deliver core HTA reports concerning the relative effectiveness assessment (REA) of pharmaceuticals.<sup>33</sup> However, a substantial part of European countries use cost-effectiveness as a criterion in coverage decisions.<sup>33</sup> Even though each EU country has its own institutions for coverage decisions, there is much to be gained from a commitment to basic principles and processes and from sharing experiences and expertise<sup>34</sup> regarding costs, as well as effectiveness. Sharing evidence tables of efficacy data used in the reimbursement assessment process of new medicines, as well as joint guideline development, could substantially improve the efficiency of reimbursement assessments in European countries.

Although there seems to be consensus on the low transferability of cost data, the increasing use of economic evaluations in decision making regarding reimbursement across Europe will most likely result in policy makers to be confronted with situations in which less than ideal evidence is available for decision making. Furthermore, if consensus could be reached on methods for both measuring and presenting data in economic evaluations such as compliance to the recommendations made by Drummond, Manca and Sculpher (2005), this could improve the ease and consistency of co-ordinating submissions for reimbursement in different European countries from the company's point-of-view.<sup>32</sup> Smaller countries could benefit especially from increasing the methods for transferability of economic evaluations as it would make submitting a dossier in these countries easier for the company. Even though there is substantial variation in the way that and the extent to which HTA and economic evaluations are applied in different European countries, their methods still have many similarities. Therefore, even though pricing and reimbursement decision making remains a national competence, there is a lot to win from a commitment to basic concepts and principles, and from sharing experiences,<sup>34</sup> explicitly as well in the measurement and transferability of cost data, to those countries that require such data for decision making.

### Methodology development: research priorities

- Support networks for cooperation and knowledge sharing among countries using HTA
- Study the transferability of economic evaluations between European countries
- Extend the activities and cooperation on relative effectiveness on relative efficacy

### Box 8.3.3: European Network for Health Technology Assessment (EUnetHTA)

Starting with the EUnetHTA project (2006-2008), the overall strategic objective of the EUnetHTA network was to connect public HTA agencies, research institutions and health ministries, enabling an effective exchange of information and support to policy decisions by Member States. The strategic objectives included to reduce overlap and duplication of efforts and hence promote more effective use of resources; to increase HTA input into decision-making in Member States and the EU and hence to increase the impact of HTA; to strengthen the link between HTA and health care policy making in the EU and its Member States; and to support countries with limited experience with HTA.

In order to continue the work initiated during the EUnetHTA Project 2006-2008, the self-funded EUnetHTA Collaboration was launched in November 2008 and ran for one year. From 2010 to 2012 the first EUnetHTA Joint Action 1 (JA1) on Health Technology Assessment (HTA) took place. A Joint Action is a cooperation between government authorities (in this case HTA agencies) and researchers and HTA institutions, institutional producers of HTA and assessments of pharmaceuticals across Europe and is co-funded by the European Commission. The overarching objective of the EUnetHTA Joint Action 1 (JA1) on Health Technology Assessment (HTA), including work on relative effectiveness of pharmaceuticals, is to put an effective and sustainable HTA collaboration in Europe into practice that brings added value at the European, national and regional level. Under JA 1, approaches were developed on how to integrate Relative Effectiveness Assessments of medicines as a special version of the HTA Core Model. The current EUnetHTA Joint Action 2 (JA2), which is scheduled from 2012 to 2015, aims to strengthen the practical application of tools and approaches to cross-border HTA collaboration. For more information visit [www.eunetha.eu](http://www.eunetha.eu)

### 2.3.4 Limited budgets

Tightening financial situations and limited budgets are a reality in many European countries, which may well result in policy makers' attention focusing primarily on cost-containment rather than rewarding innovation. Cost containment measures have been taken throughout Europe but from 2008 onwards were concentrated in Iceland, the Baltic States, Greece, Spain and Portugal – countries that have been hit hard by the financial crisis in recent years. Measures taken include price reductions, increases in the value added tax, increases in co-payments for pharmaceuticals, policies aimed at increasing generic uptake, and procedural changes, including methodological changes in the external reference price system.<sup>35</sup> In Portugal, as well as other EU countries, the Troika (European Commission, European Central and International Monetary Fund) signed a Memorandum of Understanding with the government that asked for austerity measures targeting several public sectors including pharmaceuticals. Although it is understandable that, given limited budgets, policy makers



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are focusing on cost-containment measures, there is a need to consider the long-term impact on innovation of such measures. As concerns over the long-term impacts on innovation exist,<sup>1</sup> considerations of long-term impacts should not be ignored in policy making.

Cost-containment measures in response to tightened budgets such as increased private co-payments and delisting of medicines (i.e. excluding products from public reimbursement) result in a shift of financial burden from public payers to private households. This implies the risk that patients forego needed as well as unneeded medication, discontinue treatment, or delay purchasing medicines,<sup>36,37</sup> but also aim at discouraging the unnecessary use of medicines. From 1990 onwards the share of private pharmaceutical expenditure decreased from 39% to 32% of total pharmaceutical expenditure in the EU-15 Member States, with decreases in some countries (e.g. Austria, United Kingdom, Denmark, Greece) and increases in other countries (e.g. Sweden, Italy, Portugal).<sup>38</sup> The decrease of private pharmaceutical expenditure, unless caused by changes in methodology, appears to be an encouraging trend, but data, both regarding pharmaceutical expenditure and utilization, are still missing on recent developments in order to measure the impact of the financial crisis. A WHO analysis, undertaken one year before and two years after the beginning of the recession (2007-2009), concluded that the economic recession has had a mixed effect on pharmaceutical consumption, expenditure and prices. In Europe, consumption of medicines was seen to have decreased in Baltic States and Romania while Ireland, strongly hit by the crisis, did not experience any decline in medicines consumption.<sup>39</sup> The impact of cost containment measures and the economic recession on the availability, access to and consumption of medicines, as well as potential long-term effects on innovation in European countries needs to be assessed.

### 2.3.5 Decision-making and the public debate

Payers that seek to revise their policies in order to make trade-offs between sustainability of healthcare expenditures and providing access (defined as financial access (affordability) of patients to medicines – in contrast to the word availability that is used to indicate a medicine that is marketed in a country) to medicines may meet societal opposition against such policies. Moreover, decisions to not reimburse medicines – even in light of legitimate concerns over effectiveness or cost-effectiveness - can be met with heavy criticism from stakeholders, including patients, pharmaceutical companies, and physicians. An evaluation of decision-making by the Swedish competent authority found that several stakeholders (patients, prescribers, pharmaceutical companies) actively lobbied during the decision-making process, with frequent debates in the media, with an aim to put pressure on the competent authority.<sup>40</sup> It has also been noted that in the case of stakeholder responses to decision-making in Sweden, patients might be unwilling to accept that healthcare resources are limited.<sup>40</sup>

In the Netherlands, a concept report written by the Health Care Insurance Board (CVZ) that advised the Minister of Health to no longer reimburse two orphan medicines as evidence suggested an unfavorable cost-effectiveness (the products were introduced on the market under a coverage with evidence development agreement) was leaked to the media and resulted in a heated debate on 'putting a monetary value on health'. NICE in the United Kingdom has also frequently been the topic of debate in the media. In the proposal for the United Kingdom's new value-based pricing system, it is explicitly stated that in the case the pharmaceutical company sets its price higher than would be justified by the value-based

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pricing assessment, it *'would be the company's responsibility to explain to the public why it was not prepared to offer that drug to the public at an appropriate price.'*<sup>41</sup>

Studies that have assessed public opinion on limitations of public health services due to financial constraints suggest that the public's valuation cost-effectiveness thresholds might be higher than that of policy makers.<sup>26</sup> When countries will implement decision-making processes that seek to increase efficiency in healthcare and pharmaceutical expenditures, this will almost certainly generate public debate about the societal willingness to pay for healthcare - especially if decision-making will incorporate economic criteria.<sup>26</sup> Societal learning and education regarding the rationale and importance of priority setting in healthcare could play an important role in seeking broad societal support for procedures, reimbursement criteria and decisions.<sup>40</sup> Furthermore, it will be paramount to design clear rules, procedures, and processes, in order to limit inconsistencies in decision-making and outcomes of decision-making.

### 2.3.6 Delays in access

Pricing and reimbursement procedures can result in 'delays in access' – meaning that once the medicine is given market authorization, patients have to wait until the medicine is actually available to them. Delays occur, along with other reasons, due to delays in the completion of the pricing and reimbursement process. The EC Transparency Directive<sup>18</sup> requires from Member States a pricing decision within 90 days and sets a 90-day limit on reimbursement decisions and a 180-day limit is required for joint pricing and reimbursement decisions. Authorities for pricing and reimbursement decision making have pointed out that delays in decision making sometimes occur because they have to deal with submitted dossiers that are incomplete or do not contain all information required for informed decision making.

Although pricing and reimbursement procedures play an important role in delays in access, they can be attributed to non-procedural causes as well. In some countries (e.g. Austria), manufacturers can directly supply a new medicine to hospitals without being subject to the pricing and reimbursement administrative processes, thus allowing "free pricing" to the manufacturer, while the medicine can be prescribed and has to be funded by public payers as well. Furthermore, medicines may be launched later in countries where it would be sold at a low price so as to not negatively impact the price in other countries applying external price referencing.<sup>42,43</sup> Delays in access to generics are often caused by unresolved legal patent issues. Since generics encourage competition and are seen as an opportunity to achieve savings which could be re-invested in innovation, delays of generic entry has been voiced as a concern by both industry<sup>44</sup> and countries.

The W.A.I.T. (Patients Waiting to Access Innovative Therapies) report published by EFPIA<sup>45</sup> assessed the average time between the EU marketing authorization and "patient access" – the latter being defined as the number of days until completion of post-marketing authorization administrative processes including pricing and reimbursement (but not necessarily the actual launch time). The report found an average time period between 88 and 392 days for a sample of 84 newly reimbursable medicines, centrally authorized by EMA during 2007-2009, in 14 European countries. The hospital sector is not included, however, where faster uptake may occur. The Pharmaceutical Health Information System (PHIS) project<sup>46</sup> collected data for the two time spans between the period of marketing authorization

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and pricing/reimbursement decision and between the pricing/reimbursement decision and actual marketing and data was provided by competent authorities for pricing and reimbursement. The study revealed major gaps, particularly regarding evidence on the timeline until actual market launch, and there are some variations between data of the two studies on the same time span in a country as well. Further research on the actual delays and underlying reasons is needed as a basis to identify possible ways forwards to reduce delays in access.

### Limited budgets, public debate, delays in access: research priorities

- Study the impact of the economic crisis on co-payments, financial access, utilization and consumption in all European countries.
- Study the impact of the economic crisis on innovation
- Study whether public debate influences decision-making in European countries and whether this interferes with achieving system objectives in countries or not (e.g. study biases in public perception that influence acceptance of coverage decisions)
- Assess what types of educational programs could be helpful in increasing the social support for decision-making using economic evidence.
- Identify the opportunities for patient and citizen (general public) involvement, and in what setting their contribution is of most value and needed. In this context it should be assessed what the general public and patient preferences are regarding rewarding innovation and value of medicines. For a more extensive discussion of patient and citizen involvement there is reference to Background Paper 8.5.
- Assess the extent to which delays in availability and access occurs in European countries.
- Study the causes for delays in availability and access.
- Study the availability of (new) medicines on the EU market.

### 2.3.7 Stratified medicine and medical devices

Personalized medicine has been a 'buzzword' in medicine for years, but until now, only few personalized treatments have been widely adopted in the clinic.<sup>47</sup> Personalized medicine means that a tailored approach is taken to treatment, and this approach is usually based on the molecular analysis of genes, proteins, and metabolites.<sup>47</sup> (see the Background Paper 7.4 on stratified medicines). For medicines, this usually means that a test is used to determine whether the patient will benefit from the treatment or will experience an adverse reaction.<sup>47</sup> Therefore, the term 'stratified medicine' is more appropriate, as treatments are not fully individualized but groups of patients are stratified according to having a certain characteristic.

Even though the use of diagnostics could result in lower overall costs and increased effectiveness of therapies, payers have been reluctant to invest in stratified medicine. Reasons for such reluctance include the difficulty with enforcing protocols to ensure that doctors will follow through with appropriate care based on test results, and limited control over the total costs of a diagnostic.<sup>47</sup> The cost-effectiveness of a diagnostic is driven by two main factors: per patient savings and the likelihood that the test suggests an intervention for a patient.<sup>47</sup> Tests that prevent the use of expensive treatments or delay expensive procedures

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can be very cost-effective, but diagnostics that save a small amount per patient or the characteristic that it identifies has a low prevalence among patients have a lower probability of being cost-effective.<sup>47</sup> It has been argued that value-based pricing systems, in which the price of the diagnostic and medicines are assessed simultaneously, would provide an incentive for the development of stratified medicine.<sup>48</sup>

Pharmaceutical companies have been reluctant in the development of stratified medicines for a variety of reasons, including the complex economic environment they face<sup>48</sup> and the importance of market share: a diagnostic that would identify sub-populations could decrease market share.<sup>47</sup> Notwithstanding, pricing and reimbursement issues have been identified as important factors in limiting the incentives for the development of stratified medicines.<sup>47,48</sup> Therefore, policies that enable a more viable system for pricing and reimbursement of stratified medicines are needed. Suggestions that have been made include the alignment of market authorization and reimbursement decision-making, tailored approaches to physician incentives to use diagnostics in line with recommendations, and the use of managed-entry agreements to collect additional clinical value and economic data.<sup>47</sup> Comprehensive information on how different policies stimulate or hinder the development of diagnostics and personalized medicines is currently lacking, and studying best practices might help in identifying the best approaches to pricing and reimbursement of stratified medicines.

Medical devices are much less strictly regulated than medicines in most countries. Free pricing is usually applicable to medical devices and costs are, in principle, borne by patients or – in case of hospital care – by hospitals, since there are limited medical devices reimbursement mechanisms. Furthermore, medical devices are not commonly or structurally evaluated for their (cost-)effectiveness. Yet, as some devices are high technology their use is cost-intensive and could contribute to increases in healthcare expenditures. Medical devices are important within the concept of stratified medicines (co-dependent technologies) when the “treatment package” is composed of a medicine for treatment and a medical device for diagnostic purposes. Substantial differences have been identified between European countries that have reimbursement systems for combined diagnostic and therapeutics (e.g. Germany, the United Kingdom and France) whereas for other countries (e.g. the Netherlands, Finland and Norway), no clear pathways for evaluation and funding of stratified medicine were identified.<sup>49</sup>

While pricing and reimbursement procedures are, in principle, limited to medicines, information about pricing practices and funding with regard to treatment packages involving medical devices is rare. Most countries apply price control policies for medicines but have free pricing for the diagnostic. A split in funding exists in several countries: medicines expenses are funded by the third party payers whereas tests are paid for by the hospitals, increasing the pressure on hospital budgets. Given the expected increasing importance of medical devices and diagnostics, as part of personalized medicine, policies that address reimbursement for such ‘treatment packages’ need to be developed. Furthermore, it should be assessed what the impact is of the current policies on the availability of personalized medicine therapies for patients.

### Personalized medicines and medical devices: research priorities

- Assess whether reimbursement systems of European countries have produced for medical devices and what the impact of procedures is on availability and access to medical devices.
- Assess how reimbursement frameworks and procedures could be adapted to better cope with the challenge of personalized medicines.
- Explore the need for new mechanisms, procedures and regulation with regard to stratified/personalized medicine (combination of medicine and medical device).
- Explore procedures for a common assessment of a “treatment package” (medicine and medical device).
- Assess whether price control for medical devices used in stratified medicines might be an option.
- Collect and exchange price information on medical devices and explore opportunities for a building a price database for medical devices.

## 2.4 Reimbursement outside Europe

### 2.4.1 High-income countries: Australia, Canada, New Zealand

Australia, Canada and New Zealand have a long tradition in pharmacoeconomics and HTA. Australia was the first country to require pharmaceutical companies to produce economic data in support of new pharmaceutical products on its pharmaceutical benefits scheme (PBS).<sup>50</sup> The first set of formal pharmacoeconomic guidelines were published in 1992 which, while acknowledged as a valuable tool, were critically discussed regarding the policy and methodology.<sup>51,52,53</sup> Soon after the introduction of the Australian guidelines, Canada and New Zealand followed: the Canadian Agency for Drugs and Technologies in Health (CADTH)<sup>54</sup> and the Pharmaceutical Management Agency (PHARMAC) in New Zealand published pharmacoeconomic guidelines in 1993.<sup>55</sup> This was a few years before European countries were introducing or considering requiring economic studies as a prerequisite in the reimbursement process.<sup>56</sup>

With the introduction of pharmacoeconomic principles and HTA in an increasingly number of high-income countries, there has been a large body of literature, often looking at single countries or a group of European countries, particularly United Kingdom, together with Australia and New Zealand, which addressed several of the issues which are discussed in different sections of this paper related to Europe. A 2003 OECD report on eleven OECD countries (European and non-European high-income countries) stated the benefits of pharmacoeconomic assessments for decision-making while it stressed the difficulties of determining “*an optimum amount of pharmacoeconomic assessment – that amount which balances benefits, in terms of improvements in the cost-effectiveness of pharmaceutical consumption, with costs in terms of delays in consumption and discouragement of innovation*”.<sup>57</sup>

### 2.4.2 Low- and middle-income countries

In countries without reimbursement systems in place patients pay for their medicines out of pocket. This is the predominant method of payment in most low and middle-income countries (LMIC).<sup>58</sup> Various countries have attempted to control medicine prices through a

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range of policies including setting the maximum retail prices (MRP) by using cost-plus price setting methods, or by limiting markups and margins or by reducing sales taxes.<sup>59</sup> Most surveys of medicine prices and availability have been undertaken using the WHO/HAI methodology.<sup>60</sup> Surveys performed in 36 countries (nearly all LMIC) showed that procurement prices by governments were generally close to international prices.<sup>61</sup> Public sector generic prices were three to 12 times international reference prices while private generic retail prices varied from 8.7 to 21 times the same international reference prices. Originator products were on average 2.6 times the generic prices, which makes it appear that in most LMIC prices of medicines are high in relation to purchasing power and that policy measures have generally not been effective in ensuring availability and affordability.

Some low- and middle-income countries have introduced pharmacoeconomic assessments and HTA, but it is not commonly used. There is a body of literature on the issue of pharmacoeconomics and HTA related to LMIC.<sup>62,63,64</sup> An unpublished literature review<sup>65</sup> on pharmacoeconomics and HTA as part of the WHO/HAI "Medicine Prices and Availability" project stated that a great potential for HTA to be adopted in LMIC was stressed in literature while extensive but not insurmountable barriers were identified. Among those barriers it was noted that resources required to implement pharmacoeconomics are significant, including the establishment of a regulatory system, and it was recommended to start early and support capacity building for HTA in LMIC. Further, the review indicated that the use of pharmacoeconomics would require the introduction of new legislation to formalize the process. It was suggested that LMIC should learn from countries where pharmacoeconomics and HTA are well established, while in turn countries advanced in pharmacoeconomics and HTA were asked to share guidance and expertise and be transparent.

A lack of quantitative evidence was identified concerning the impact of pharmacoeconomics and HTA on prices, reimbursement and access to medicines – not only for LMIC, but also for high-income countries with established pharmacoeconomic systems and asked for research performed in comparison with other pricing policies or generic promotion.<sup>65</sup> Since studies could not provide a clear answer regarding the generalizability and transferability of health technology assessment results from high-income countries to LMIC, the applicability of pharmacoeconomic standards across countries and settings would require further research. However, given the difference in the health systems and cost bases, the transferability of HTA evaluation from high-income countries to LMIC can be questioned. Furthermore, the lack of reliable data and the variability of the functioning of many individual health systems in LMIC could undermine the assumptions that would have to be made and lead to at least sub-optimal and at worse damaging outcomes for patients.

### **3. Managing price and volume**

The reimbursement of medicines in Europe was discussed in the previous section, including a number of key developments and challenges for reimbursement systems. The increasing use of HTA and economic evaluations in the assessment and appraisal of medicines is a clear trend in Europe, and could aid countries in aligning potentially competing policy objectives of rewarding innovation, cost containment, and access to medicines. A reimbursement policy based on HTA and economic evaluations alone however, will not be sufficient for resulting

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long-term positive effects of rewarding innovation. Several additional conditions need to be met, most importantly in the way prices of medicines are set and in the way price and volume of medicines are controlled, if payers want to be successful in controlling pharmaceutical expenditure while simultaneously seeking ways to stimulate pharmaceutical R&D. The price of medicines is a crucial factor in both the control of pharmaceutical expenditure as well as profits generated from marketed medicines to determine whether returns on investments are sufficient to stimulate future R&D in areas of unmet medical needs and/or future medical needs. In this section, pricing practices are discussed including their effects, and several key developments in pricing policies.

### 3.1 Pricing policies and their effects

#### 3.1.1 Pricing policies

Setting the price of medicines can either be left to the pharmaceutical industry and/or a stakeholder in the supply chain (free pricing) or can be performed by the state (price control). Usually, in the European Union, price control is applied for “reimbursable medicines”, i.e. those funded, at least partially, by public payers, while free pricing is common for non-reimbursable medicines.<sup>66</sup> In case of price control, different methodologies may be applied. A very common pricing policy is benchmarking of prices, which means that either the price of the same medicine in other countries (external price referencing) or - in case of competitor products available - the price of identical/similar medicines in the same country (internal price referencing) are used as a benchmark for the medicine’s price. External price referencing is the predominant pricing policy in Europe (see below). For internal reference pricing, medicines are usually grouped based on the Anatomical Therapeutic Chemical (ATC) codes (different chemical structure but with the same indication). In pharmacoeconomic assessment the price of a pharmaceutical depends on its cost-effectiveness<sup>15</sup> (see section on value-based pricing).

#### 3.1.2 External price referencing

External price referencing is defined as “*the practice of using the price(s) of a pharmaceutical product in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country*”.<sup>67,68</sup> In 2013, this practice is used in 24 out of 27 EU Member States<sup>69</sup>, and it is also continuously gaining relevance worldwide.<sup>67</sup> (see also the section on the rest of the world). There are a large number of variations in the way external price referencing is designed and implemented in the European countries (Table 8.3.1). External price referencing does not necessarily target all (new) medicines: In European countries external price referencing is usually applied to on-patent medicines which are considered reimbursable whereas off-patent medicines may be subject to internal price referencing (see the section on generics and on the rest of the world). It should be noted that in some European countries external price referencing is not the sole pricing policy, but the price of the medicine in other countries is one of several criteria in the price setting process (Table 8.3.1).

Evidence on the impact and limitations of external price referencing is scant (even for the European countries though literature is focused on these countries). This was also a finding of a literature review under the WHO/HAI Pharmaceutical Pricing Project.<sup>67</sup> Most studies are descriptive, and very few evaluated the impact of the policy. Usually, only the impact on

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prices is assessed – within the country applying external price referencing and possible spillover effects to other countries. Håkonsen et al (2009)<sup>70</sup> looked at medicines prices development from 1994 to 2004 in Norway, which had introduced external price referencing in 2000, and claimed that consistent use of external price referencing and subsequent price revisions led to substantial price reductions on many medicines. Windmeijer et al. (2006)<sup>71</sup> measured the effects of the implementation of external price referencing in the Netherlands and came to the conclusion that this pricing practice resulted in lower prices. Merkur and Mossialos (2007)<sup>72</sup> simulated the effect of external price referencing on medicine prices in Cyprus and showed that this would lower prices and contain costs after identifying Cyprus as a high price country for medicines. Filko and Szilagyi (2009)<sup>73</sup> stated that due to the policy change of external price referencing in Slovakia in 2009, the proportion of pharmaceutical expenditure as share of total health care spending declined by approximately 25 per cent showed in a study on 14 European countries that for patented medicines, prices are in general lower in cases where the country applied external price referencing compared to countries which did not.<sup>74</sup> Nevertheless substantial price differences among countries that apply EPR were identified. Stargardt and Schreyögg (2006)<sup>75</sup> looked into how the composition of the country basket and possible price reductions have an influence on the price level in other countries: A price reduction of €1.00 in Germany was found to reduce maximum reimbursement prices from €0.15 in Austria to €0.36 in Italy.

Despite these indications that the policy may appear to be able to drive prices down, external price referencing has been criticized for several reasons, among those for its potential to discourage innovation and impede patient access.<sup>27</sup> A major argument against external price referencing is that it neither reflects the willingness-to-pay nor the ability-to-pay of a country, which other concepts such as value-based pricing do. By setting the price of a new medicine based on the price of that same medicine in a number of other countries, a country would only end up with a price that offers both value for money as a reward for innovation if all referenced prices would be value-based. However, the widespread use of external price referencing provides a pharmaceutical company with an incentive to first launch its product in 'free-pricing' countries (such as the United Kingdom, Denmark, Germany), where they are likely to obtain high price, and to delay launching the product in low-price markets.<sup>1,76</sup>

It is often argued that, if all European countries apply external price referencing and they all refer to each other, eventually the price level across Europe will converge.<sup>1,67,77</sup> Currently, however, price variances across Europe continue to exist (see also the table on price data in the Annex 8.3.2). These price differences are likely the result of different methodologies that are used for external price referencing. For example, not all countries use the same basket of countries that are referenced, and where some countries reference the lowest price in the country basket, others reference the average price.<sup>77,78</sup> With regard to price convergence, there is no clear picture for Europe: two recent studies, which tested the price convergence in European Union,<sup>79,80</sup> suggested no substantial reduction in price dispersion within the EU countries. These findings differ from previous results which indicated for price convergence within the European Union for newly launched medicines.<sup>81</sup>

The referencing across countries is nearly always done to the list prices of medicines. In practice, *actual* prices in European countries tend to be lower than list prices due to arrangements between industry and payers, whose provisions are usually kept confidential (see section on discounts & rebates). Since countries will continue to refer to the higher list prices indicated in the price data bases instead of the actual discounted prices, they might



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risk overpaying. Further, the implementation of discounts and rebates offered by industry to public payers in order to avoid statutory cuts of list prices is likely to prevent a transfer of possible savings of price cuts in one country to the reference countries. An analysis on the impact of price cuts in Greece and Spain<sup>35</sup> showed that the price reductions were not automatically translated into price decreases in referencing countries as expected, which could either be due to countries not regularly monitoring the medicines prices in the other countries, or the confidential discounts and rebates which were not reflected in the list prices. This also highlights the complexity in applying external price referencing: apart from identifying and obtaining access to relevant data sources, capacity has to be built on understanding the different price types applied and included in the national databases and on identifying the limitations of the data sources (e.g. inclusion of outpatient sector and/or reimbursable medicines only, no discounts and rebates reflected). Furthermore, regular monitoring on the changes in the prices in other countries, including in distribution mark-up regulation, is needed – given that ex-post adaptations of prices are possible. This makes external price referencing both time and resource-intensive.

External price referencing is still a reality in European countries, particularly for pricing new medicines, and it is generally expected to continue to play a role. Notwithstanding this observation, in 2010 a World Bank expert predicted that external reference pricing would soon reach the end of its useful cycle, as when almost all countries reference each other, prices will converge and price differences between countries will diminish.<sup>82</sup> Whether this prediction will turn out to be accurate remains to be seen for now.

**Table 8.3.1: Different methodologies applied for external price referencing in EU Member States**

Country	Relevance of EPR	Scope	Country basket: number of countries included	Calculation of benchmark price
Austria	Main policy / criterion	Reimbursable medicines	24	Average of all countries
Belgium	Supportive information	All medicines	24	Average of all countries
Bulgaria	Main policy / criterion	Prescription-only medicines	9	Three lowest prices
Cyprus	Main policy / criterion	Imported medicines	4	Average of all countries
Czech Republic	Main policy / criterion	All medicines	26	Average of all countries
Denmark	Not applied			
Germany	Not applied			
Estonia	Main policy / criterion	Reimbursable medicines	-	-
Greece	Main policy / criterion	All medicines	22	Three lowest
Spain	Main policy / criterion	Innovative medicines	Not defined	Not defined
Finland	Main policy / criterion	Reimbursable medicines	16	Checking prices of reference countries in a specific order
France	Main policy / criterion	Innovative medicines	4	Prices not higher than

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				in the reference countries
Hungary	Main policy / criterion	Reimbursable medicines	24	Lowest price of the basket
Ireland	Main policy / criterion	Prescription-only medicines	9	Average of all countries
Italy	Supportive information	Reimbursable medicines	Not defined	Average of all countries
Lithuania	Main policy / criterion	Reimbursable medicines	4	95% of average in reference countries
Luxemburg	Main policy / criterion	All medicines	1	Lowest price per basket
Latvia	Main policy / criterion	Reimbursable medicines	3	Third lowest price, not higher than price in Lithuania and Estonia
Malta	Main policy / criterion in the private sector		26	
Netherlands	Main policy / criterion	Prescription-only medicines	4	Average of reference countries
Norway	Main policy / criterion	Prescription-only medicines	9	Average of three lowest countries
Poland	Main policy / criterion	Reimbursable medicines	17	Lowest price per basket
Portugal	Main policy / criterion	Prescription-only medicines	4	Average of reference countries
Romania	Main policy / criterion	Reimbursable medicines	12	Lowest price per basket
Sweden	EPR not applied			
Slovenia	Main policy / criterion	Reimbursable medicines	3	95% of average of countries
Slovakia	Main policy / criterion	Reimbursable medicines	26	Average of 6 lowest countries in the basket
United Kingdom	EPR not applied			

Sources: Carone G, Schwierz C, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. European Commission, Directorate General for Economic and Financial Affairs, 2012.<sup>1</sup>

Leopold C, Vogler S, Mantel-Teeuwisse AK, de Joncheere K, Leufkens HG, Laing R. Differences in external price referencing in Europe: a descriptive overview. Health Policy 2012 Jan;104(1):50-60<sup>78</sup>

### External price referencing: research priorities

- To study the effect of external price referencing on innovation, timely access to medicines, and sustainable funding
- Study the impact of external price referencing on incentives for R&D
- Assess whether there is evidence of price convergence following the use of external price referencing
- Explore to what extent EPR can achieve intended effects and to what extent methodology improvement are possible
- Study the impact of confidential discounts and rebates applied in external price referencing
- Explore the role of price information systems and regular price reviews
- Assess spill-over effects of external price referencing on the availability and prices in lower income countries.

### 3.1.3 Value-based pricing

‘Value-based pricing’ means that the price of a medicine is set according to the value it generates and is an alternative to external price referencing. Value-based pricing is gaining momentum, although there is no widely-accepted definition of value in this context.<sup>27</sup> Sweden, Canada and Australia have already implemented value-based pricing systems<sup>83</sup> and the United Kingdom will implement a new value-based pricing system, set to replace the 50-year old Pharmaceutical Price Regulation Scheme (PPRS) in 2014.<sup>41,83</sup> The United Kingdom’s value-based pricing system will focus on quality-adjusted life year (QALY) gains in relation to costs, although considerations related to innovation, burden of illness, and rare diseases might be addressed in decision making as well.<sup>83</sup> Sweden abolished external price referencing and introduced a value-based pricing system in 2002 (see Box 8.3.3), which uses priority setting in healthcare on considerations of human dignity, need and solidarity, and cost-effectiveness.<sup>40</sup> Given that value-based pricing is a policy that has not seen widespread uptake as of now, much of the evidence for its ability to align policy objectives remains theoretical at this point, even though inferences based on economic theory and modeling approaches have indicated that value-based pricing could result in both static and dynamic efficiency.<sup>84,85</sup>

Value-based pricing for medicines means that in price setting for new medicines, prices are set based on the value the medicine offers, usually, as assessed through health technology assessment (HTA) or economic evaluation.<sup>86</sup> However, there is no widely accepted definition as to what types of policies are in fact value-based pricing systems – the OECD very recently assessed the value-based pricing elements of several countries, and concluded that all countries included have a system in place that assesses the added value of pharmaceuticals,<sup>27</sup> but not all countries included (Australia, Belgium, Canada, France, Italy, Norway, the Netherlands, Sweden, and the United Kingdom) have fully integrated pricing and reimbursement decisions. In the United Kingdom (at the time of the study) the price is negotiated through the PPRS and routine HTA of all pharmaceuticals is not performed. Furthermore, the majority of the studied countries in the OECD report use external price referencing for setting prices.<sup>27</sup> A ‘narrow’ definition is applied for value-based pricing as to not confuse the reader, and do not define systems that use HTA to inform reimbursement

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decisions but where price setting occurs separately, from systems in which pricing and reimbursement decisions are fully integrated. According to this definition of value-based pricing, only a few countries worldwide use value-based pricing today (in Europe: Sweden, and the United Kingdom from 2014 onwards), whereas most European countries use HTA primarily as part of reimbursement (and not pricing) decisions. This narrow definition is used as systems that have value-based elements in their reimbursement processes (such as the use of economic evaluations to inform decision-making) still can use pricing policies such as external price referencing for setting prices.

When value is determined by the incremental cost-effectiveness of a new medicine in value-based pricing, information on a new medicine's incremental health gains ( $\Delta E$  and incremental costs ( $\Delta C$ ) over an existing treatment options is required to determine the amount of added value of the new medicine. In 'normal' cost-effectiveness analysis the ICER is usually expressed as costs per QALY gained. The decision maker subsequently will determine whether the ICER is deemed acceptable or not. An explicit willingness to pay threshold ( $k$ ), however, is required in value-based pricing in order to determine the pharmaceutical's price. When the decision maker has access to all information on costs and health effects, given the formula  $k = \Delta C / \Delta E$ , and given that  $\Delta C$  is composed of both price (the unknown) and all other costs (defined), determining the value-based price would be a matter of simply solving the formula. Furthermore, given that the total budget impact of a newly introduced medicine consists of both price and volume, value-based pricing enables the decision maker to derive a 'menu' of combinations of prices and volumes – given that a number of sub-populations and indications can be identified for the medicine.<sup>85</sup>

One of the main criticisms of value-based pricing is that by using an explicit threshold (also see the discussion on willingness to pay in the previous section), manufacturers will have no incentive to price their product below the threshold.<sup>83</sup> Although this is true, there are several reasons why such a mechanism is actually considered preferable; firstly, as the price of a new medicine will depend on the additional value it generates, it will allow medicines that generate more health gains to capture a larger price, which will create an incentive for the development of products that generate more added value – and will create a disincentive for the development of products for indications that already have (good) treatment options. Secondly, as the market exclusivity for new medicines is limited, there will be positive net benefits in the long run to the healthcare system as the price of a medicine is expected to drop once generic competitors enter the market due to price competition. Therefore, although no net benefits occur short-term, there will be substantial net benefits once the patent expires – given that the medicine has a long life cycle and is not replaced by innovative medicines in the near future.<sup>83,85</sup>

Another main argument for allowing manufacturers to price at the threshold is that it will result in both static and dynamic efficiency<sup>84,85,86</sup> allowing all value to be appropriated by the manufacturer during the patent life of the medicine will provide an incentivized innovation in the long run.<sup>85,86</sup> A value-based pricing system that is properly and consistently applied could therefore result in allocative efficiency, and could create sufficient incentives to pharmaceutical companies in the long term for the investment in the development of new medicines. Furthermore, value-based pricing would create a clear incentive to companies for the investment in therapeutic areas of unmet medical needs and in therapeutic areas that have no or ineffective treatment options only. Finally, strategic launching behavior and

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delays in access could be reduced as the necessity to rely on external price referencing to set prices would disappear in countries that would introduce value-based pricing.

It is recognized, however, that in order to achieve positive long-term effects, certain conditions need to be met: cheaper generics will enter the market after patent expiration, prescribing will switch to the generic versions, and future patented medicines reflect their value compared to the (cheaper) generic versions of the old branded medicine.<sup>85</sup> The rationale of the use of an explicit willingness to pay threshold that allows manufacturers to price a new medicine to the point where the net benefits are zero (i.e. where the incremental cost-effectiveness ratio of the new medicine equals the threshold) is to provide access to new medicines at a price that is socially acceptable, rewarding companies for innovation, while positive net benefits will be achieved for the healthcare system in the long run (i.e. after market exclusivity ends). Furthermore, it has been argued that value-based pricing holds several advantages over currently used pricing systems, as it is expected that a country's willingness to pay will be based on citizens' willingness to pay for medical care, which is related to a country's per capita GDP – meaning that if multiple countries would implement value-based pricing, it would allow for differences in prices according to differences in willingness and ability to pay between countries.<sup>84</sup> However, the existence of parallel trade could substantially hinder the successful implementation of value-based pricing. This issue is covered further in this section.

### 3.1.4 Priority setting using value-based pricing

In order to create financial incentives for priority medicines, payers could consider the advantages of value-based pricing combined with a societal perspective. If a payer would make explicit statements about its willingness to pay threshold for a new treatment indicated for Alzheimer disease, or depression, this would clearly signal to pharmaceutical companies that for these indications, treatments that result in significant therapeutic improvements, significant cost savings, or both, would be rewarded with a premium price. Allowing a pharmaceutical company to capture all benefits during the period of market exclusivity, as has been proposed in the United Kingdom, will create an incentive for the development of priority medicines.

A study that assessed the reimbursement systems of five European countries concluded that all systems included in their analysis were mainly supply-driven, and that a shift towards reimbursement policies that are more pro-active should be considered.<sup>16</sup> Most decision-makers are not explicit about the types of medicines that they would like to be developed and these are not considerations that are usually taken into account; the pharmaceutical industry determines what medicines are and are not developed. Value-based pricing could facilitate a shift as it provides companies with an incentive to develop products that do not only result in health benefits, but that also prevents costs – either related to illness or broader societal costs (when a societal perspective is taken). Payers could make their demand for certain medicines explicit through their willingness to pay for certain indications. The Swedish value-based pricing system, that uses a societal perspective, allows for economic benefits to be captured in the price (see Box 8.3.2). It has been assessed that for Alzheimer disease, direct medical costs account for 10 to 25% of all costs, whereas indirect costs account for 8 to 79% of all costs.<sup>27,87</sup> A review of economic evaluation of treatments for depression showed that productivity costs (indirect costs) accounted for 60% of total costs in studies that used a societal perspective.<sup>88</sup> There are substantial savings possible therefore in both

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therapeutic areas, which means that, if payers would allow such benefits to be captured in the price, incentives could be created for the development of medicines for these conditions. Methods to set value-based prices using economic evaluations should be developed.

### Value-based pricing: research priorities

- Study and evaluate the impact of value based pricing on innovation aligning with other policy goal such as access to medicines and cost-containment
- Explore which prerequisites needs to be met for achieving the intended results
- Accompany and monitor the implementation of this policy when newly introduced (e.g. the United Kingdom)
- Method development for value-based pricing should be supported
- Study how societal preferences regarding rewarding innovation can be reflected through value-based pricing systems such that thresholds reflect societal preferences
- Study barriers to implementing value-based pricing

### 3.1.5 Differential pricing

Patents and data exclusivity create a temporary monopoly for a company, which means that pricing is not influenced by the presence of competitors. Given the large fixed costs of pharmaceutical R&D, a period of market exclusivity enables a company to charge prices that are higher than they would be in a competitive market and to generate profits that earn back investments and generate funds for future R&D.<sup>43</sup> Although patents result in high prices, a company that seeks to maximize profits would ideally launch a medicine in multiple countries, where national prices depend on the country's ability to pay.<sup>43</sup> The cost of R&D is a fixed, globally joint cost for a pharmaceutical company. This means that R&D costs do not depend much on the number of countries where the medicine eventually will be launched, or on the number of people that will ultimately use the medicine.<sup>43</sup> Therefore, once a medicine has been launched in several countries, there is no large incremental R&D expense to launch the medicine in additional countries – and the other costs of launching the product in a country are relatively low.<sup>43</sup> The concept of Ramsey optimal pricing states that prices should differ across markets according to the demand elasticity: more price-sensitive users are charged a lower price than users that are less sensitive. In practice, this means that users in lower income countries usually pay a lower price as they are more sensitive to price than high-income users.<sup>43</sup>

When a company charges a different price to different groups of consumers for reasons not related to costs, this is called price discrimination or differential pricing. 'Differential pricing' therefore is not so much a pricing policy (such as external price referencing or value-based pricing) but an economic concept. Differential pricing therefore could be pursued simultaneously with value-based pricing. An essential requirement for companies to engage in differential pricing, however, is that markets need to be sufficiently separated.<sup>89</sup>

Differential pricing is limited within the EU market for two main reasons. First, within the European Union, the legal concept of 'exhaustion' restricts differential pricing as exhaustion means that once a patented product is marketed, the company no longer has control over the distribution of the product.<sup>90</sup> As the European Union follows the concept of EU-wide

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exhaustion, which is tied to the free movement of goods,<sup>90</sup> the parallel trade of medicines throughout the EU is possible. Parallel trade occurs when products are legally imported from another country without the authorization of the manufacturer.<sup>91</sup> Price differentials are the driving forces of parallel trade: when price differences between countries are large enough, it will be profitable for a wholesaler to import medicines from low-price countries.<sup>90</sup> Parallel trade within the EU severely restricts the possibilities for differential pricing, resulting in reduced patient access in poorer countries.

A second main limitation to differential pricing in the Europe is the widespread use of external reference pricing, which is used by almost all European countries to some extent.<sup>6</sup> As a result, pharmaceutical companies will seek a similar list prices across countries that are linked by referencing, 'first launch' in markets where less restrictive pricing mechanisms are used, and will have an incentive to either delay the launch of a medicine in low-income countries, or will not launch in these countries at all,<sup>84</sup> especially if the low-price countries are small markets<sup>84,92</sup>, although it has been suggested that the causes of observed launch delays could be multi-factorial.<sup>93</sup>

The effects of parallel trade and external price referencing are not shared equally between high-income countries, low-income countries, and pharmaceutical companies, but are most likely to result in reduced social welfare in the relatively lower income countries<sup>91</sup>: given linkage of markets through parallel trade and external price referencing, it is against a company's interest to launch a medicine in a market where the country's affordability would result in a price low enough to initiate parallel trade to markets with high prices or that would substantially lower prices in other markets through external price referencing. Additionally, in response to parallel trade, pharmaceutical companies are more likely to bargain for a higher price in low-income countries than they would under a regime where parallel trade was not possible.<sup>91</sup> In contrast, for high-income countries the effects of price inter-dependency through parallel trade and external price referencing are more positive, as it will result in lower prices than without the existence of inter-dependencies.<sup>84,91</sup> Even though throughout Europe price differences are still observed, there may be reason for concern regarding the access to medicines in EU countries with lower income levels – as well as those European countries that have been affected by the economic crisis.

A shift from external reference pricing towards value-based pricing - where prices for new pharmaceuticals would be set based on added value in relation to an explicit threshold - has been proposed to replace external reference pricing policies, in order to allow differential pricing and achieve both static and dynamic efficiency.<sup>2,84</sup> However, even if all countries in Europe would implement value-based pricing systems, this would not resolve the issue of parallel trading that could still distort the intended effects of any value based pricing policy.

Without a substantial change to the legal EU framework there are only two mechanisms that could allow differential pricing for medicines in Europe. First, within the current systems, European countries could consider revising their basket of reference countries and remove those countries that do not have comparable GDP per capita, as it would reduce the incentives for pharmaceutical companies to not launch, delay launch, or negotiate high prices in the lowest income countries. A second possibility is for lower income countries to agree to a high list price for new medicines, while negotiating confidential discounts and rebates with pharmaceutical companies.<sup>84</sup> Confidential discounts and rebates are currently the only instrument available to achieve differential pricing, and to help assure that citizens

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of European countries with lower affordability for medicines will maintain access to medicines, and mechanisms such as confidential discounts and rebates are necessary to achieve separation of markets under external price referencing and parallel trade.<sup>89</sup>

The previous Priority Medicines Report proposed to explore a value-based pricing system where the threshold for each country would be based on the national income level.<sup>94</sup> The authors of the background paper 'Approach to the valuation and pricing of future medicines' argued that it was unfair to expect R&D costs to be spread equally across countries of variable wealth,<sup>94</sup> and therefore a country's threshold or ability to pay should be based on its GDP per capita. Such a system of differential pricing (or 'equity pricing') would be an '*equitable system for true innovation while ensuring access by those who need them*'.<sup>94</sup> The variations in GDP per capita throughout the EU are substantial: the average EU-27 capita was €25 200 in 2011, but GDP varies from €9 800 in Latvia to €82 100 in Luxembourg. There would need to be a major political commitment from European countries in order implement such a system, and any country that would not participate could 'free-ride' by letting other countries reward innovation while setting lower prices.

### Differential pricing: research priorities

- Evaluate the impact of EPR and parallel trade, in terms of availability of medicines and the affordability of medicines in EU countries.
- Study mechanisms through which differential pricing could be applied to the European market
- Explore the prerequisites that are needed to support differential pricing

### 3.1.6 Volume control and incentives for prescribing/dispensing

Historically, payers' focus has primarily been on controlling pharmaceutical prices. In recent years, however, it has been increasingly acknowledged that pharmaceutical expenditure is not merely determined by *price* but is mainly driven by *volume* (see Figure 8.3.1). Pricing policies therefore are one of several variables influencing profitability of investing in pharmaceutical R&D. Policies that influence volume, as well as generic promotion policies influence market exclusivity, enforcement, and therefore could impact incentives for innovation.<sup>2</sup>

Furthermore, in many cases the incomes of health care providers (in particular pharmacists) are linked to discounts, rebates and dispensing fees. This can have a positive impact, by creating the right incentives for rational use of medicines, but it can also have adverse effects by creating a stimulus for inappropriate use of medicines, or create a threat to the economic sustainability of health care providers (e.g. if incomes are linked to certain margins on products, and these margins are excessively reduced).

A key volume-control policy concerns the monitoring of the prescription behavior and nowadays all EU Member States have some type of prescription monitoring system in place. The Danish electronic monitoring system (Ordiprax, [www.ordiprax.dk](http://www.ordiprax.dk)) is an example of a prescription monitoring system that allows the authorities to assess pharmaceutical consumption at the central, local and the individual physician level. Doctors have access to



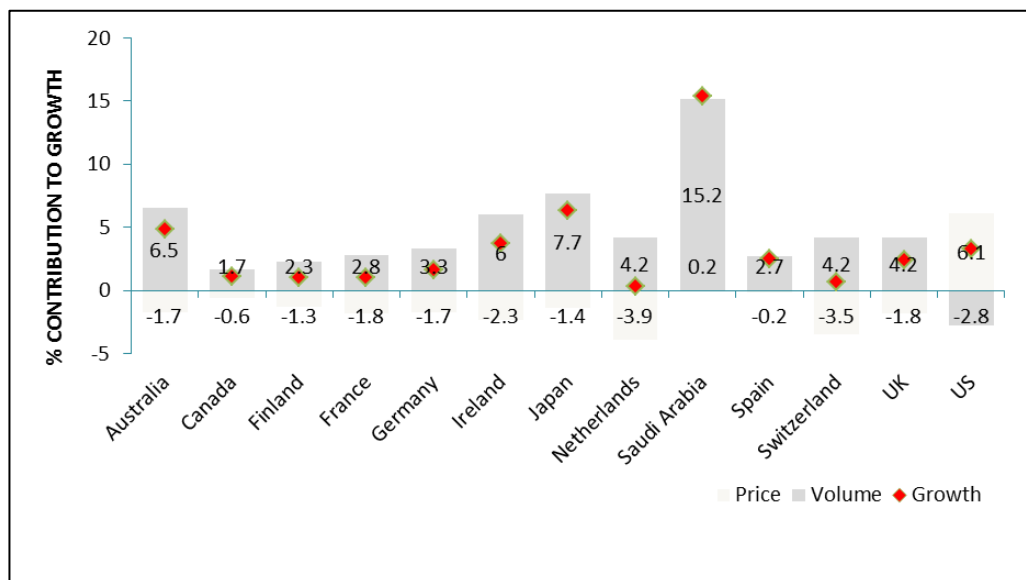
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the Ordiprax system as well, enabling them to compare their prescription pattern to other physicians in the region.<sup>95</sup> Some European countries supplement prescription monitoring with specific doctor agreements, such as an obligation to prescribe a specific amount or less expensive medicines. Furthermore, several European countries (Czech Republic, Latvia, Slovakia, United Kingdom, some regions in Spain and Sweden) have pharmaceutical budgets for prescribers in place.<sup>95</sup> Budgets can be combined with financial incentives, for example doctors may keep some of the savings to invest into their practice (e.g. “Indicative Drug Target Scheme” in Ireland whose financial incentive had meanwhile been abolished), or could face penalties in case of excess (e.g. Latvia). During the 1990s, more European countries (e.g. Germany, and France) had pharmaceutical budgets in place that yielded expected savings the first year after introduction but lost their effectiveness in subsequent years - as announced sanctions could not be executed resulting in the abolishment of pharmaceutical budgets in these countries.<sup>96</sup> Although France and Italy nowadays do have targets regarding prescribing limits, they are officially not called budgets.<sup>95</sup>

### Volume control: research priorities

- Study the impact of the volume component on pharmaceutical expenditure, innovation and access to medicines
- Explore how policies aimed at controlling volume, including different incentives targeted at various stakeholders, can be designed to ideally not only contain pharmaceutical expenditure, but also encourage a more rational use of medicines
- Study how an “ideal policy mix” addressing both price as well as volume can be designed

Figure 8.3.1: Elements of Growth in 2011 – High income countries



Source: IMS MIDAS, Dec 2011

Note: Growth refers to full 2011 growth over 2010 in constant US dollars. Price growth reflects growth due to price differences for packs sold in 2011 compared to their prices in 2010. It is measured in constant US dollars at the ex-manufacturer level. Volume growth is often referred to as sales at constant prices at the ex-manufacturer level and refers to growth due to changes in the packages sold by applying 2010 prices to volumes in both 2010 and 2011. It is measured in constant US dollars at the ex-manufacturer level.

### 3.2 New trends in pricing and reimbursement

#### 3.2.1 Use of managed-entry agreements in Europe

At the time that reimbursement is sought for a new medicine, overall evidence might be insufficient to accurately assess the clinical effectiveness, cost-effectiveness, or budget impact of a new medicine in clinical practice. As more countries start to use HTA in reimbursement decisions, the lack of long-term data available at the time of market introduction, especially for chronic therapies, becomes more problematic.<sup>97</sup> The added value of medicines for chronic diseases is usually driven by projections on long-term health outcomes, which means that extrapolations based on surrogate endpoints in Phase III trials will have to be made. If such evidence is not accepted by payers and most countries do not accept price increases after product launch, this forces companies into a trade-off of launching earlier at a lower price or delaying launch in order to collect the required evidence that might result in a higher or premium price and delayed access for patients.<sup>97</sup> Managed-entry agreements between payers and companies could, at least partially, solve this issue<sup>97</sup> as they enable the decision-maker to grant access to a new medicine under certain restrictions that are either aimed at reducing this uncertainty or transferring the risk associated with the uncertainty to the manufacturer.

Therefore, in recent years agreements between payers and industry intended to manage such uncertainty have gained importance. These different approaches have been summarized under the concept of “managed-entry agreements” (MEA). In managed entry-agreements, a major distinction can be drawn between arrangements based on *outcomes* (e.g. coverage with evident development (CEP), patient access schemes (PAS), risk-sharing schemes (RSS), conditional reimbursement, outcome guarantee arrangements) and *non-outcome* based arrangements (e.g. price-volume agreements, utilization caps). Managed-entry agreements allow for a medicine to enter the market subject to certain restrictions of conditions. These conditions are usually related to tracking the actual utilization or performance of the medicine or to tie the level of reimbursement to a defined outcome.<sup>98</sup>

Managed-entry agreements have been introduced in several European countries, particularly in the United Kingdom, Belgium, Italy, Poland, and the Baltic states. A study by Kanavos et al.<sup>99</sup> (unpublished) studied various managed-entry agreements in Europe and found that 75% of all the agreements in the studied countries aimed to address budget impact, either alone (42%) or in combination with cost-effectiveness (16%), use (15%) or both (2%). Two main trends in European countries employing managed-entry agreements seem to emerge: a focus on budget impact, or on cost-effectiveness. Managed-entry agreements in countries such as Italy, Portugal, Lithuania, the Czech Republic, and Belgium primarily focused on budget impact, whereas cost-effectiveness seemed to be the driving force in countries like Sweden, the Netherlands, and the United Kingdom, when deciding to engage in managed-entry agreements. The most commonly found types of managed-entry agreements were price-volume agreements (40%), followed by requirements for data collection (29.4%), and limited access to eligible patients (12.6%). Price-volume agreements are widely used in Italy, Portugal, and Lithuania while data collection is a common requirement in Italy, the Netherlands, the Czech Republic and Sweden. Italy, the Czech Republic and Belgium limit access to eligible patients in an attempt to manage budget impact and use. In terms of therapeutic groups, antineoplastic and immune-modulating agents represented 37.3% of all the managed-entry agreements identified by Kanavos et al<sup>99</sup>, followed by alimentary tract and metabolism (16.5%) and nervous system agents (9.8%). In all EU Member States apart

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from Sweden, the greatest proportion of agreement involved antineoplastic and immunomodulating medicines.

Klemp et al. (2011)<sup>98</sup> provided an overview of advantages and disadvantages of managed-entry agreements to different stakeholders. The main disadvantages included the costs and bureaucracy required for the implementation of agreements to both companies as well as for payers. Furthermore, for the payer it could be costly and time-consuming to manage multiple schemes. An important disadvantage for a payer, furthermore, is the difficulty to withdraw reimbursement or coverage once certain outcomes are not confirmed. It might prove to be quite difficult to withdraw a medicine once it is made available, and doing so would require clear rules and procedures<sup>98</sup> – as well as public and stakeholder support for such procedures.

It has been argued that managed-entry agreements are essentially a warranty offered by the manufacturer of a medicine – typically for new and expensive medicines.<sup>100</sup> As the manufacturer can in some circumstances, be in a better position to be confident about the benefits of its product, a managed-entry agreement can be used to offset some of the risk to the payer that cannot be sure about the performance of the medicine in clinical practice.<sup>100</sup> However, in the case of the performance of a medicine in clinical practice there is much uncertainty that neither the manufacturer nor the payer are able to reduce. It has been argued, therefore, that managed-entry agreements that seek to limit the exposure of a payer by limiting payment to specific subpopulations or at given prices to unexpectedly *valuable* innovations, can limit incentives to invest in the development of costly and high risk indications.<sup>100</sup> Although for payers, managed-entry agreements are a good method to reduce the risk of undesirable outcomes (i.e. higher volumes or less health benefits than anticipated), payers have to be prepared to allow companies to reap the upside surprise of a medicine that performs better than expected<sup>100</sup>, as otherwise incentives to develop products for high-risk indications might be limited.

Managed-entry agreements are usually confidential. Therefore, an important incentive to engage in managed-entry agreements, other than market access, would be to limit spillover effects to other markets as a result of parallel trade and external price referencing, This does, however, have implications for transparency (see later discussion on transparency).

### **Managed-entry agreements: research priorities**

- Assess the effects of managed-entry agreements, as there is limited evidence on the impact they have on prices, availability, access, and incentives for innovation.
- Support the exchange of best practices between countries
- Explore the prerequisites for the implementation of managed-entry agreements, and assess for which medicines they appear most appropriate

### **3.2.2 The role of the hospital setting and interface management**

Several innovative medicines tend to be used in the hospital setting, frequently for hospital-exclusive use. Until recently the expenditure of medicines in hospitals has not been a priority for policy makers as the expenditure of medicines in hospitals has been fairly constant and

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relatively low (usually between 5 and 10 per cent of a country's pharmaceutical budget) over the years. The introduction of expensive new medicines, including orphan medicines, has resulted in disproportional increases of hospital pharmaceutical budgets and raised the attention of policy makers in recent years.<sup>101</sup> Additionally, it is increasingly recognized that pharmaceutical treatments that start in hospitals influence the medication used in the outpatient sector.<sup>102,103,104,105,106</sup>

Published information about pharmaceutical pricing practices, medicines management and medicines prices in hospitals in European countries was not available until recently since most research about medicines policies has concerned the outpatient sector only, although there was widespread anecdotal knowledge about discounts on medicines prices in the hospital sector. Policy makers tended to have very limited knowledge about the inpatient sector as well, as national competent authorities in European countries are usually responsible for deciding prices and reimbursement coverage of medicines used in for the outpatient sector only. Medicines used in hospitals are usually financed through hospital budgets (and not by the payers for outpatient medicines), and their procurement and listing on the hospital formulary is not the responsibility of the competent authorities but of hospital pharmacists.<sup>107</sup>

Given this lack of knowledge, there has been a call for examining medicines management and prices in the hospital setting.<sup>66</sup> In response the Pharmaceutical Health Information System (PHIS) project surveyed the pricing and procurement practices and funding models for medicines used in hospitals in European countries (see Box 8.3.4 for procurement methods and Table 8.3.2 for new funding mechanisms for high-cost medicines, see the section on new funding mechanisms). Though prices of medicines used in hospitals are usually linked to confidentiality issues, making it difficult to assess actual prices, the PHS study surveyed official hospital list prices and actual prices paid by hospitals in five European countries. The results confirmed the existence of discounts and rebates granted to specific medicines for hospital use. While hospitals appear to have little headroom to negotiate price reductions for medicines to which no therapeutic alternatives are available, high price reductions, including cost-free provision of medicines (if allowed by national legislation), tend to be granted to medicines whose treatment is likely to continue in primary care after discharge of the patient.<sup>107</sup> The results suggest the need to bridge the gap between the outpatient and inpatient sectors both for (innovative) high-cost medicines - since otherwise payers will have an incentive to find arguments why medicinal treatment might be shifted to the other sector - as well as for high volume medicines to which pharmaceutical companies are likely to grant to hospital pharmacists large discounts and rebates, in order to facilitate starting treatment in hospitals.

Given the complex situation and different incentives to stakeholders; policy makers and stakeholders have been urging for an improvement of medicines management at the interface,<sup>108</sup> but knowledge about good practice examples appear to be scant. There appears to be two different approaches to improve the "interface management" (of note: there are different terms to address such initiatives at the interface between primary care and hospitals. Other common terms are seamless care, continuous care, transitional care, transmurial care, integrative care. The different notions and terms also confirm that the cooperation mechanisms between hospital and outpatient sector can still be further explored). Firstly, measures might be set at a micro-level of individual hospitals and consist of cooperation with outpatient carers, including interventions at admission and particularly

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hospital discharge (e.g. communication of discharge information to general practitioners and community pharmacists, education and pre-discharge pharmaceutical counselling of patients, community liaison service, home visits by a health visitor shortly after discharge, a follow-up phone call by a pharmacist, computer-based interventions).<sup>109,110</sup> Secondly, at the system level, the organisation and funding of the pharmaceutical system could be addressed. Such measures would imply legal and organisational changes. Though few European countries have implemented such system-related interface management policies<sup>107</sup> there are some good practice examples such as the joint reimbursement lists and joint Drugs and Therapeutics Committees in the Stockholm County in Sweden<sup>111</sup> and Scotland<sup>112</sup>. Interface management measures addressing the organisation and funding of the system are likely to be supportive to improve access to medicines, since they no longer incentivize individual payers and procurers to pay attention to the sector only for which they are responsible for but decisions taken would automatically impact both sectors.

### **Box 8.3.4: Procurement practices for medicines used in hospitals in European countries**

The PHIS project identified tendering and negotiations as the most important procurement policies in the European hospital setting, whereas procurement by competitive negotiations is rather rare. For example, it is used in Slovakia via what is known as “market evaluation” in which hospital pharmacists always ask three suppliers for a cost estimate.

Many European countries apply a mix of purchasing policies. In some countries tendering is the sole or key policy for procuring medicines. In eight countries (Cyprus, Estonia, Italy, Latvia, Malta, Norway, Sweden and the United Kingdom) all or the majority of medicines used in (public) hospitals are put out to tender. Tendering may be done by the hospitals (individually or by the organization owning the hospitals) or centrally, usually carried out by Ministries of Health, social health insurance institutions or procurement agencies. Well-known examples for the latter case are the national procurement agencies AMGROS and LIS in Denmark and Norway, in charge of procuring all medicines for public hospitals. In Romania and Slovakia tendering is done centrally for some, mostly expensive medicines such as blood factors, while other medicines are procured via direct negotiations between the hospitals and the pharmaceutical companies or wholesalers.

Several countries have established regional procurement committees (e.g. the Regional Therapeutic Committees in Italy or joint municipal authorities for primary healthcare in Finland), which are responsible for purchasing medicines for hospitals. Hospitals may join purchasing groups that procure together and that are formed by hospitals in the same region or under the same management.

There is a trend for more acquisitions to be made by tendering. Several Western European countries reported tendering being used for most acquisitions, while direct negotiations by hospitals with suppliers (e.g. manufacturers or wholesalers) are the key purchasing policy in Austria, Germany and some countries in Central and Eastern Europe.

*(Source: Vogler et al. 2010, PHIS Hospital Pharma Report)<sup>107</sup>*

### 3.2.3 New funding mechanisms

Innovative medicines are often high cost medicines and as such, put pressure on healthcare budgets. As a response, payers throughout the EU have sought for new solutions that would ensure financial access to these medicines and as a result have proposed various new funding mechanisms. This section lists a few examples that were implemented in recent years.

Some European countries have implemented joint funding mechanisms for specific high cost medicines that usually provide that outpatient payers (partially) fund the in-hospital use of high-cost medicines (see Table 8.3.2 for some examples from European countries). The rationale for co-sharing of costs by the hospitals in some of the model is that hospitals should be encouraged *“to use these medicines in an efficient way”*.<sup>107</sup>

In 2011, England established a Cancer Drugs Fund, which has injected £200 million of additional funding into England’s NHS each year to fund new cancer medicines not recommended by NICE. Scotland made a new £21 million fund available for orphan medicines that are not recommended by the Scottish Medicines Consortium (SMC) which will become operational during 2014. All regional health authorities for England’s Cancer Drug Fund, together with an expert panel, developed a “priority list” of cancer medicines to be included. Since its inception, a total of 34 medicines have been made available through this fund, and by December 2011 the fund approved treatment for almost 10 000 cancer patients.<sup>113</sup> The effects of England’s Cancer Drug Fund are not clear. It has been argued that the existence of the fund could lead to NICE’s Appraisal Committees being more likely to refuse new cancer medicines, knowing that the fund will provide access for those patients most likely to benefit. Furthermore, the presence of the fund may encourage manufacturers to set the prices of new cancer medicines higher than they otherwise would have as the Cancer Drug Fund does not incentivise lower prices.

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**Table 8.3.2: New funding mechanisms across outpatient and hospital sectors**

Countries	Special funding mechanism
Austria	At the time of the study, in two provinces in Austria (Styria, Carinthia) the main public hospital owner organisations have concluded agreements with the regional sickness funds stating that the expenditure of selected high-cost medicines (e.g. oncologic medicines) used in hospitals are funded differently. In these provinces will be covered by the sickness fund even if they are dispensed in the inpatient sector.
Bulgaria	Some medicines for treating particular diseases in hospitals are paid for through the state budget.
France	A supplementary list, "liste en sus" or "non T2A" medicines, of high-cost medicines excluded from the DRG system (particularly anti-cancer medicines, blood products, orphan medicines and some treatments for rheumatoid arthritis) has been developed. Medicines on this list are reimbursed up to 70 to 100% separately by the social health insurance. Another list of "reassigned medicines" which may be dispensed to outpatients by hospitals is reimbursed by the sickness fund.
Germany	For high-cost medicines additional reimbursement based on the documentation of their use.
Hungary	Anti-coagulant factors are centrally procured products.
Latvia	Certain high-cost medicines may be covered by the state budget.
Netherlands	Orphan medicines on the orphan medicine list and expensive medicines on the list of high-cost medicines (both lists set up by the Dutch Health Care Authority) are reimbursed by the health social insurance: 100% for orphan medicines, and 80% for expensive medicines, the rest is of the cost is borne by the hospitals.
Poland	Highly specialised services (e.g. grafting, incl. pharmaceutical treatment) are funded by the state budget.
Slovenia	High-cost medicines (e.g. infliximab, rituximab, alemtuzumab, docetaxel) are not part of the hospital budget. The Health Committee evaluates on a case per case basis high-cost medicines and prepares the proposal whether to financed for inpatient treatment (i.e. financing of certain indications for a determined number of patients by a certain scheme in a specific hospital e.g. university hospital, specialised hospital). The final decision of financing of high-cost medicines for hospital use is made by agreements between representatives of hospitals, the Health Insurance Institute and the Ministry of Health. On the basis of these annual agreements, the Health Insurance Institute finances the specific high-cost medicine for a specific hospital.
Slovakia	Some medicines like growth factors or beta-interferons are purchased by sickness funds directly in case medicines are used in special limited centres in hospitals.

Source: Vogler S, Habl C, Leopold C. et al. PHIS Hospital Pharma Report 2010. Pharmaceutical Health Information System. Available at:

[http://ec.europa.eu/health/healthcare/docs/phihospital\\_pharma\\_report\\_en.pdf](http://ec.europa.eu/health/healthcare/docs/phihospital_pharma_report_en.pdf).<sup>107</sup>

Please note that these are specific funding mechanisms on top of the general funding in hospitals which, in the countries presented, provides for funding of medicines out of the hospital budget. Expenses for medicines are part of the general payment scheme (usually a DRG system).

The Italian fund for encouraging independent research, established with the Italian Medicines Agency (AIFA) was created in 2005 and is funded by pharmaceutical manufacturers that are required to contribute five per cent of their expenses in promotional activities.<sup>114</sup> Several AIFA activities are funded from this ear-marked money but the major aim of this ad-hoc fund, which consists of about €40 million each year, is "to support clinical

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*research on drugs in areas of interest for the National Health Service (NHS) and where commercial support is normally insufficient*".<sup>115</sup> Areas in which research is stimulated include patient populations normally excluded by clinical studies such as children, pregnant women, and the elderly. Other main research areas are orphan medicines, head-to-head comparisons, strategies to improve the rational use and pharmacoepidemiological studies. AIFA launches yearly calls for proposals aimed at researchers in the public sector.<sup>115</sup>

Most of these new funding mechanisms have not been evaluated yet, so it is unclear whether such mechanisms reach intended goals, or what unintended consequences of such policies are.

### **Hospital setting, new funding mechanisms: research priorities**

- Assess actual hospital prices in countries.
- Identify and evaluate existing initiatives to improve medicines management at the interface of the primary and hospital sector with regard to their impact on access to medicines, adherence, cost-containment and innovation
- Explore barriers and opportunities for cooperation at the interface of the primary and hospital sector and develop a "tool box" for a successful implementation of such a new model.
- Evaluate new funding mechanisms, including prize funds, with a focus on their ability to create incentives for R&D in areas of unmet medical needs.
- Identify best practices in new funding mechanisms.

### **3.2.4 Generic promotion as pharmaceutical policy option**

In recent years, European countries have implemented a number of measures to capture the potential value, in terms of cost savings, created by patent expiration leading to the subsequent market entry of generic medicines stimulating their appropriate use. Yet, in many European countries opportunities still exist to either speed up generic entry, increase generic consumption and/or lower the prices of generic medicines, as substantial differences remain in generic entry, uptake and prices, compared, for example, with the United States.<sup>116</sup> Savings could create "headroom for innovation" and partly be used to facilitate uptake of, or rewards for, innovative medicines.

Policies aiming at encouraging generics uptake can be successful in both containing prices and public pharmaceutical expenditure growth.<sup>1,2,66,117 ,118</sup> Savings generated by generic promotion policies can free resources that, in return, could be used to finance access to new innovative medicines. Initiatives to promote generics uptake include a range of policy options and in European countries a range of generic policies are applied, although their design and number vary among the countries. Internal price referencing, which consists of pricing a medicine according to the prices of either identical or similar products marketed in a country, is the most frequently applied practice with regard to generics. Countries may opt for setting the price of the generic medicines at a certain percentage below the price of the originator. Sixteen out of 29 European countries (27 EU Member States plus Croatia and Norway) apply this generic price link policy.<sup>119</sup> Since 2005, Norway has used the 'stepped price model' (Trinnprismodellen) to incrementally reduce the price of off-patent medicines



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according to predefined rates, depending on sales volumes, with the first reduction occurring after a medicine has lost patent protection.<sup>120</sup> Countries that do not have a generic price link policy but rather relied on competition to reduce generic prices have been found to have larger price differences among generics, compared to countries with generic price policies.<sup>121</sup>

Twenty years ago only Germany, Denmark, the Netherlands and Sweden used internal reference pricing systems. At the beginning of 2013, all EU Member States except Austria, Cyprus, Malta, Luxemburg, Sweden, and the United Kingdom have a system in place in which groups of identical or similar medicines are clustered in order to fix a maximum reimbursement amount (so-called reference price) to be covered by the third party payer.<sup>69</sup> A sufficient number of generics or other alternative medicines on the market in order to build a cluster is required for an internal reference pricing system to function properly. This may explain why in several European countries a reference price system was only introduced during the last 13 years, although strong opposition to the introduction of such a system might delay the implementation as well.<sup>122</sup>

Major demand-side measures to enhance generics uptake include generic substitution and INN prescribing. Generic substitution means that the pharmacist substitutes the prescribed medicine by another, usually less expensive medicine containing the same active ingredient(s). INN substitution concerns physicians prescribing active ingredients instead of brand names. An increasing number of European countries have introduced generics substitution and/or INN prescribing, and in several remaining countries possible introduction has been discussed.<sup>119</sup> In the 27 EU Member States, generics substitution is in place in 20 countries (all but Austria, Bulgaria, Cyprus – private sector, Greece, Ireland, Luxembourg, and the United Kingdom), and INN prescribing is in place in 22 countries.<sup>119</sup> Most European countries have implemented generic substitution and/or INN prescribing on a voluntary basis but in recent years, Lithuania, Slovakia, and Italy changed from indicative to mandatory INN prescribing.

Financial incentives to enhance generics uptake are not very common in the European countries. Italy applies a different mark-up for originator medicines and biosimilars compared to generics as an incentive to pharmacists<sup>69</sup> and in France a pharmacist will receive the same amount of money for dispensing a generic as the original medicine<sup>123</sup> In the Netherlands, the opportunity for the pharmacist to keep a third of the savings achieved by generic substitution was abolished in 2004.<sup>119</sup>

### 3.2.5 Tendering

A major change that has occurred since the publication of the previous Priority Medicines Report in 2004 is the introduction of tendering systems in the outpatient sector in several European countries. The best-known example is the Dutch preference pricing policy, but other countries have also introduced tendering-like elements in their pricing and reimbursement practices for medicines in the outpatient sector.<sup>124</sup> Under the Dutch preference price policy, which was introduced in 2005 by five health insurers and has been extended ever since, health insurance companies determine one or a limited number of medicine(s) per cluster consisting of medicines with the same active ingredient, dosage form and strength, as preferred for a fixed time period of usually six months. The preferred medicine is determined through a tendering process, and only the medicine that wins the

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tender will be reimbursed.<sup>125</sup> The preference pricing policy was considered as very successful; initial total savings (projected to €355 million annually) exceeded expectations since the preference policy scheme resulted in fierce price competition among generic companies.<sup>126</sup> However, while the saving potential of tendering has been shown in several cases, its long-term effects are still unclear. As there have been reports of short-term absences of some medicines due to logistic shortages,<sup>117,122,126</sup> an important drawback of tendering could be the increased risk of shortages.

### Generics policies, tendering: research priorities

In the area of new trends in pricing and reimbursement the following have been identified:

- Explore best practices in generics policies, including the design of tendering in order to prevent shortages.
- Study reasons (system, cultural, other) for differences in generic uptake between countries
- Study the impact of tendering with regard to price and expenditure development, accessibility and availability of medicines in the market, and the implication of these developments on innovation
- Explore how generic policies can enhance innovation.

## 3.3 Current and future challenges for pricing and reimbursement

### 3.3.1 Orphan medicines

Rare diseases are severe medical conditions that affect a low number of patients. A range of special regulations have been adopted in order to stimulate the development of medicines for rare diseases – called orphan medicines.<sup>127</sup> These regulations have been successful in stimulating the development of orphans, as it is expected that the hundredth orphan medicine will reach market authorization in the EU in the period of 2012 to 2014 and the two-hundredth in 2017.<sup>127</sup> However, given the limited market size for orphan medicines, many orphans fail to meet standards for cost-effectiveness of medicines.<sup>128</sup> A main challenge for policy makers faced with coverage decisions of orphan medicines, concerns the question whether in the allocation of healthcare resources, special considerations (with regard to cost-effectiveness) should be made for patients with rare diseases.<sup>129</sup>

If orphan medicines are reimbursed at much higher incremental cost-effectiveness than would be considered acceptable for medicines indicated for more common diseases, this would be in violation of the equity principle, as it would imply that a patient with a common definition and who would acquire the same health gain is less worthy of receiving treatment<sup>129</sup> and from a utilitarian point-of-view, it would be unethical to invest substantial amounts of resources for the rare conditions as this would not maximize society's benefits.<sup>129</sup> However, under EU legislation individuals are entitled to a decent minimum of healthcare, which could require that treatment is made available for orphan diseases, but it has been questioned whether orphan disease pose such an imminent threat to a patient's health to constitute such a rights-based approach.<sup>129</sup> It has been noted, however, that the mere fact that orphan medicines are reimbursed in many countries demonstrates that budget impact,

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clinical effectiveness, and/or equity issues are all weighed more than cost-effectiveness in coverage decisions.<sup>129</sup>

The low budget impact of orphan medicines might contribute to many orphans receiving reimbursement, regardless of high incremental cost-effectiveness ratios. In the Netherlands, for example, the total costs of all outpatient orphan medicines were estimated at €170 million in 2011<sup>130</sup> whereas the total costs of all outpatient medicines were estimated at €5.2 billion, which means that the orphan medicines expenditures make up less than 4% of the total pharmaceutical expenditures. However, the total orphan expenditure increased by 12% as compared to 2010, whereas the total pharmaceutical expenditure only increased with 0.2% in 2011.<sup>130</sup> Furthermore, it has been estimated that the costs of inpatient orphan medicines totaled about €90 million in 2011.<sup>130</sup> Although the contribution of orphan medicines in terms of pharmaceutical expenditures are relatively minor, total expenditure is increasing – and at a higher rate than total pharmaceutical expenditure. Given the expected numbers of orphan medicines reaching the European markets the coming years, attention of policy makers is required concerning the cost-effectiveness of orphan medicines.

Given the especially small markets for orphan medicines, cooperation between countries in collecting data needed to inform reimbursement decisions of orphans might be warranted, especially for smaller countries. As the low number of patients is a barrier to collect sufficient data regarding clinical effectiveness and costs of treatment, cooperation could result in increased efficiency of the reimbursement process of orphan medicines in Europe. Furthermore, countries could assess together, based on the combined market potential, what type of reward for innovation would be appropriate – by doing so, the responsibility for rewarding innovation through prices could be assessed on an international level instead of the national level. Also, see the background paper on orphan medicines.

### 3.3.2 Discounts and rebates

Price reductions can take different forms; they might be discounts (i.e. price reductions granted to specified purchasers under specific conditions prior to purchase) or rebates (i.e. payments made to the purchaser after the transaction has occurred), medicines can be provided cost-free to purchasers, or the strategy of bundling is applied where several products for sale are offered as one combined product.<sup>68</sup> Usually, discounts and rebates agreements are kept confidential. Managed-entry agreements, such as price-volume or risk-sharing agreements (see the section on managed-entry agreements) may also be also be considered as forms of discounts and rebates though the presence of such agreements is usually not kept confidential.

The existence of discounts and rebates granted by suppliers has been long known, at least at an anecdotal basis, for the hospital sector. The findings from the EU PHIS project confirmed that some medicines used in hospitals, particularly those with therapeutic alternatives and which are likely to be used for long-treatment after discharge of the patient from hospital, are supplied to hospitals at high discounts and even for free in those European countries where such practices are allowed.<sup>107</sup> This practice of granting high discounts on these typically high volume medicines is more likely to occur when the organization of the pharmaceutical system has different payers for the outpatient and inpatient sector. Its effect on shifting of costs, treatments and thus patients among the sectors were discussed in the section on the hospital setting and interface management.

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In the outpatient sector, discounts and rebates have been used by stakeholders in the supply chain to compete on prices, particularly on generic medicines.<sup>117,118</sup> Additionally, discounts and rebates granted to public payers in the outpatient sector have been increasingly playing a role in Europe (see also the sections of other high-income countries). According to a recent survey<sup>131</sup>, in 25 of 31 surveyed European countries discounts and rebates are granted to public payers by pharmaceutical companies, in the outpatient sector in 21 countries, and in the inpatient sector in all 25 countries.<sup>131</sup> The most common discounts and rebates consist of price reductions and refunds linked to sales volume, but in-kind support, price-volume and risk-sharing agreements were identified as well, and in general, a mix of various types of discounts and rebates is common.

It has been argued that discounts and rebates would offer advantages to the various stakeholders as discounts and rebates serve cost-containment purposes for payers (“hidden price cuts”) and they allow pharmaceutical companies to gain market share. Furthermore, the argument has been raised that for countries that have a limited ability to pay and are included in the reference baskets of other countries, confidential discounts and rebates are a tool to increase access to patients, as under full transparency, companies might be less willing to launch a product in their country or might insist on a higher price.<sup>84,92</sup> Managed-entry agreements allow for the management of uncertainty and offers patients access to new medicines whose effectiveness has not been fully established (see also the section on managed entry agreements).

However, since discounts and rebates are in most cases confidential, this has implications for transparency. Given the widespread use of external price referencing in European countries (see the section on external price referencing) and the fact that discounts and rebates have been increasingly demanded as a kind of “hidden price cuts” instead of real price cuts<sup>69</sup>, it creates a situation in which the surveyed list prices may provide at best only an indication of, but not a reflection of actual prices. As a result, confidential discounts and rebates limit the opportunities for cost savings for countries that use external price referencing (see also the section on external price referencing) and refer to the list prices indicated in the national price databases. There is no evidence as to whether discounts and rebates have any effect on innovation. Furthermore, the belief that confidential agreements might result in better prices has not been confirmed. On the contrary, there is evidence from the hospital sector that all hospitals were offered the same prices under confidential agreements, and the extent of discounts and rebates did not vary among hospitals but was dependent on the existence of therapeutic alternatives.<sup>107</sup>

### **Orphan medicines, discounts and rebates: research priorities**

- Study the societal support for high prices and high incremental cost-effectiveness of orphan medicines.
- Study the ability for a cooperative structure in data collection for cost-effectiveness evidence between countries
- Assess the extent to which discounts and rebates are used in European countries, and what are the implications for the countries applying the policies and the other countries.

### 3.4 Managing price and volume outside Europe

High-income countries outside Europe use similar pricing and reimbursement practices to those applied in European countries. New Zealand uses a system of contracts between the public purchaser, the Pharmaceutical Management Agency of New Zealand (PHARMAC), and manufacturers. The contracts include rebates on list prices, tendering for off-patent medicines, and bundle agreements where PHARMAC may list expensive new medicines in return for the manufacturer discounting the price of other products it supplies.<sup>132,133</sup>

A pricing policy frequently used in several low- and middle-income countries world-wide is cost-plus pricing.<sup>134</sup> This is the practice of calculating the medicine price based on the production costs, promotional expenses, research & development, administration costs, overheads and profit.<sup>68</sup> Cost-plus pricing depends on accurate information on material prices and cost data provided by the manufacturers, which is difficult to obtain. There is a lack of evidence supporting the use of cost-plus formulae, as there is a lack of published evidence on the impact of this pricing policy in general.<sup>134</sup>

Meanwhile, several countries, particularly middle-income countries, have moved to implementing external price referencing. As for high-income countries (see section on external price referencing), there are variances in the design of this pricing practice. In several LMIC external price referencing tends to be applied to be both on-patent and off-patent medicines, whereas in high-income countries the latter are usually subject to internal price referencing. Possible effects and limitations of the external price referencing practice were already discussed under the external price referencing section for the European countries, and they are also relevant in this context. Studies on the impact of external price referencing, particularly on prices beyond the national borders, are rare.<sup>67</sup>

In many low- and middle-income countries, the provision of a usually limited range of medicines in public sector facilities is procured by the state. While eligible patients can access essential medicines in the public sector either free of charge or with a modest co-payment, they have to purchase out-of-pocket medicines in the private sector.<sup>61,135</sup> World Health Survey data show that about half (41% and 56%) of households in LMIC spend all of their health expenses on medicines.<sup>136</sup> A major concern for LMIC is to ensure access to essential medicines. It was argued that the effect of price regulation on innovation is probably not a main concern, as these countries do not often have an innovative pharmaceutical industry.<sup>67</sup> Moreover, the impact of regulation in a single low- or middle-income country on innovation is considered as negligible since innovation is usually led by global market trends.<sup>2,67</sup> However, the level of medicines prices have an implication on availability since low medicines can reduce the attractiveness of certain countries to manufacturers and importers which might result in important products not being produced and marketed in a particular country or at least, being marketed with substantial delays.<sup>67</sup>

As an approach to address this challenge of limited availability, differential pricing was proposed. Differential pricing, tiered pricing or Ramsey pricing, means that different prices are applied for different purchasers (see section on differential pricing). For more than a decade it has been discussed as a possible solution, particularly in the international context, as an alternative to high prices when separated high- and low-to-middle-income markets exist for a medicine and when the seller exerts significant power over pricing, such as when there is limited or no competition due to patent protection, data exclusivity, or other market-

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entry barriers.<sup>43</sup> In the Priority Medicines Report 2004, such an approach with thresholds (of maximum prices per medicine as determined by economic evaluation) for each country based on the national income level<sup>94</sup> was proposed as a way forward to enhance innovation and provide access to medicines, particularly for middle-income countries. Recently, the MIT Zaragoza center reviewed existing knowledge and expertise and did not find a widespread use of differential pricing. A systematic use of differential pricing has been limited to vaccines, contraceptives, and antiretrovirals (ARVs) mostly in low income countries.

Although differential pricing is not a panacea to ensuring access, it can benefit manufacturers and poor countries without adversely affecting higher income countries. More research is needed in order to understand on how differential pricing can be expanded to include all essential medicines for low- and middle-income countries and how fair, affordable prices should be determined<sup>137,138</sup>. Moon et al. (2011) examined international drug medicines developments for antiretrovirals, artemisinin combination therapies, drug-resistant tuberculosis medicines, liposomal amphotericin B (for visceral leishmaniasis), and pneumococcal vaccines and found several shortcomings in differential pricing.<sup>138</sup> It was considered as inferior to competition for achieving the lowest sustainable prices; it often involved arbitrary divisions between markets and/or countries leading to very high prices for middle-income markets; and it left a disproportionate amount of decision-making power in the hands of sellers vis-à-vis consumers. Still, the authors argued that in special cases – such as when market volumes are very small or multi-source production capacity is lacking – differential pricing may offer the only practical option to meet short-term needs for access to medicines.<sup>138</sup>

Another issue that needs attention regarding medicine prices in LMIC is different add-ons, including mark-ups, duties, tariffs, and taxes, which increase the end price for the patient considerably. Thanks to the WHO/HAI work on medicine prices, availability, affordability and price components, there is evidence about the existence and amount of these add-ons, which are high compared to European countries.<sup>139</sup> But there is paucity in information about the impact of these add-ons regarding utilization and access to medicines.<sup>140,141</sup> A major argument against taxes, duties and tariffs is that it is a regressive form of taxation that targets the sick, and there has been a call for eliminating these taxes on essential medicines without adverse revenue or industrial policy impacts.<sup>141,142</sup> As far as attention to mark-ups and margins are concerned, care must be taken to ensure that incentives to reach rural and hard to reach patients are not reduced thereby exacerbating lack of access to these groups. In LMIC there has been limited experience with value based pricing policies though South Africa has announced their intention to utilize this approach as a part of their price control regimen.<sup>143</sup>

Promotion of the use of quality-assured generic medicines has great potential to reduce medicine prices to consumers in LMIC. Cameron et al using demonstrated that in 17 countries, savings of between 9% and 89% were possible.<sup>144</sup> In practice however, branded generic medicines frequently dominate the market in LMIC and their prices may be set closer to originator than generic prices. Such patterns also occur in high-income countries.

### 4. Networks and infrastructure

#### 4.1 Collaborations on the European level

In the following, some initiatives, projects and networks will be presented which are examples of collaboration in the field of pharmaceutical pricing and reimbursement among European countries. In addition, cooperation also occurs in the field of market authorization, for instance with the Head of Medicines Agencies<sup>145</sup> but this is not scope of this chapter. A possible bridging between marketing authorization and pricing and reimbursement will be addressed in the sub-section on relative effectiveness cooperations.

##### 4.1.1 European processes regarding pricing and reimbursement

In the year 2000, concerns were raised regarding the competitiveness of the European pharmaceutical industry lagging behind the United States.<sup>146</sup> In response, The European Union established the G10 group - ten selected Member States and stakeholder representatives - who presented recommendations on how to enhance competitiveness and innovation in the pharmaceutical sector in Europe in 2002.<sup>147</sup> To follow up on these recommendations, the High Level Pharmaceutical Forum was set up in 2005 as a three-year process. The Pharmaceutical Forum focused on three main topics: information to patients on diseases and treatment options, pricing and reimbursement policies, and relative effectiveness. For each of these topics a Working Group was set up. The Relative Effectiveness Working Group for example set out core principles on relative effectiveness assessments<sup>148</sup> that could be relevant for developing national systems and would help to encourage of exchange of information, methodologies and experiences between the relevant national authorities.

After the Pharmaceutical Forum, the European Commission followed the recommendation for a continuation of cooperation and sharing of experiences at the EU level the network of Competent Authorities for Pharmaceutical Pricing and Reimbursement (CAPR) was set up, and the Process on Corporate Responsibility in the field of Pharmaceuticals was launched with three independent platforms. The platform "Access to medicines in Europe" was *"dedicated to enhance voluntary collaboration among the Member States and relevant stakeholders in order, when appropriate, to find common non-regulatory approaches to enable timely and equitable access to medicines after their marketing authorization"*<sup>149</sup> Its six working groups have been addressing orphan medicines, biosimilars, over-the-counter medicines, supply in small markets, managed-entry agreements and prioritization (Priority Medicines Report). The outcomes of the five first working groups of Platform on Access to Medicines in Europe have been finalized and were endorsed by the Steering Group in April 2003.<sup>150</sup> A more in-depth description of the processes at EU level, including key conclusions of policy papers and recommendations, is provided in the Annex 8.3.1.

##### 4.1.2 Networks of competent authorities for pricing and reimbursement

The first European network of competent authorities for pharmaceutical pricing and reimbursement information is the Pharmaceutical Pricing and Reimbursement Information (PPRI) network. This resulted from an EC / DG Health and Consumers co-funded project (2005 to 2008) which collected and analysed pharmaceutical pricing and reimbursement

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information about countries by producing more than 20 country reports, a set of indicators for comparison pharmaceutical systems, a glossary of pharmaceutical terms and a benchmarking report.<sup>151</sup> The technical deliverables such as the country reports or outcomes of internal queries have produced an evidence base as a basis for further research<sup>152</sup> The participating members of the competent authorities see as the major value of PPRI its contribution to *“to improve the exchange of information between the Member States”*.<sup>153</sup> For this reason, PPRI has continued after the end of the EC funding as an informal network of public authorities of pharmaceutical pricing and reimbursement borne by the commitment of all participants, with a financial contribution of Austria for the PPRI secretariat. The PPRI network currently involves around 70 institutions (mainly relevant authorities and third party payers) from 40 mainly European countries, as well as European and international institutions (European Commission services, OECD, WHO). Under the Pharmaceutical Health Information System (PHIS) project the PPRI project was extended to hospital pharmacists and experts.<sup>154</sup> In 2007, the CAPR (Competent Authorities for Pricing and Reimbursement of Pharmaceuticals) network was set up. No public information is available on CAPR. According to delegates who are members of both the PPRI and CAPR network, PPRI is considered as a network of technical staff who deal with pricing and reimbursement decision on a daily basis and benefit from the cooperation from the experiences from the other countries, whereas the CAPR network is rather seen as a strategic group. In order to support the CAPR network, the European Medicines Information Network project (EMINet) was launched in December 2008 to provide information, technical expertise and analysis on pharmaceutical pricing and reimbursement policies and related topics such as the distribution or rational use of medicines during 2009 until 2012.

Further networks have been established which also address pricing and reimbursement issues. The “Piperska group” was set up in 2008, as an informal network of European reimbursement authorities and researchers, with the aim of enhancing a more rational use of medicines.<sup>155</sup> Members of the European Social Insurance Platform (ESIP), which is a strategic alliance of over 40 national social insurance organisations across Europe ([www.esip.org](http://www.esip.org)), form the MEDEV (Medicines Evaluation) group whose members (staff of social insurance taking reimbursement decisions) meet several times a year to share information about assessments of medicines<sup>156</sup> The value of these networks has been generally acknowledged and the need for the cooperation and exchange of experiences has been expressed in several policy documents.<sup>147</sup> To the authors’ knowledge, the PPRI/PHIS network was the only one being evaluated. The evaluation report<sup>157</sup> highlighted the value of the network as most outstanding achievement. This report quoted an interviewee who said that *“the value of the network as a global model remains very attractive”*. The network was reported to serve a good practice model, e.g. it was used in the Western Pacific region for sharing public sector procurement information.

### 4.1.3 Cooperation on relative effectiveness

The most prominent EU network in the field of Relative Effectiveness is the EC-supported European Network for Health Technology Assessment (EUnetHTA). EUnetHTA has seen different phases of organisation and cooperation structure during the last decade (see Box 8.3.3). EUnetHTA was identified as an appropriate candidate for developing scientific recommendations for improvements in relative effectiveness assessment, and it developed the HTA Core Model (<http://www.eunetha.eu/hta-core-model>). This is a guidance document for producing extensive multi-dimensional assessments of health technologies that are



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reported in a structured format and that can be used as a foundation for local, e.g. national or regional, health technology assessment reports.

Further major cooperation in the field of relative effectiveness is the informal cooperation between HAS (France), IQWiQ (Germany) and NICE (United Kingdom) for exchanging experience in the evaluation of medicines, the AGREE cooperation, aiming at improving the quality and effectiveness of clinical practice guidelines by establishing a shared framework for their development, reporting and assessment<sup>158</sup>, and Guidelines International Network (G-I-N, <http://www.g-i-n.net/>) for promoting systematic development of clinical practice guidelines. The ADVANCE-HTA project co-funded by the EC (FP 7) is a consortium of 13 institutional partners lead by LSE Health that aims to advance and strengthen the methodological tools and practices relating to the application and implementation of HTA. In the project, issues such as value for money, concepts of value assessments, methods associated with the assessment of rare diseases and elicitation of preferences are addressed.<sup>159</sup>

While there has been a call for more studies which support payer's decision on reimbursement and more exchange of information on relative efficacy<sup>160,161</sup>, there are no explicit cooperation structures known in Europe. This might be a task for existing networks to address this issue as well as work on bridging between regulatory authorities and payers.

### 4.1.4 Medicines price databases

In Europe, work on building a database which contains medicines prices began in the late 1990s. The initial project, Ecpin, with institutional support from the Commission's Joint Research Centre, set out to create a database on the basis of voluntary contributions from Member States and built the technical basis. Within the framework of the next project, EudraNet, it was then fed with price data from Member States, however stopped after some time. The European Commission explained that due to the data delivery at different times and by different means, it was difficult to undertake comparisons.<sup>162</sup>

Based on a decision in the EU Transparency Committee (a consultative committee established based on the EC Transparency Directive), EU Member States agreed in 2005 on sharing medicines prices for a selected range of medicines. The INFOPRICE exercise was done on a bi-annual level. It was stopped at the end of 2012 to avoid redundancy since a European medicines price database (EURIPID) has meanwhile been set up.

This EURIPID medicine price database is currently (2009-2013) established, with the support of an EC grant. It is led by a project consortium of Hungary and Austria and it contains data provided from Member States. In its report as of 25 January 2013 on the proposal for a Directive of the European Parliament and of the Council relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems, the European Parliament advised the Commission and the Member States to *"examine how to continue to co-operate on the functioning of the EURIPID price information database, which provides EU-wide added value in terms of price transparency"*.<sup>163</sup> However, the sustainability of the EURIPID is not yet known.

The EURIPID medicines price database complements existing national price information systems and databases, which are offered either by commercial providers or have been

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established by competent authorities for pricing which require price information for external price referencing. Most of the authorities' price information systems of authorities are for internal use only. One example of a publicly available service is Pharma Price Information (PPI, <http://www.goeg.at/en/PPI>) of Gesundheit Österreich GmbH (Austrian Health Institute) which, in accordance with the Austrian Social Insurance law, provides price data for 30 countries. The service started as support to the Pricing Committee of the Austrian Federal Ministry of Health but data allocated can be provided to all interested parties in order that no party would be excluded, however without financial burden for Austrian authorities.

In LMIC, tender price and government procurement price data has been available for nearly 30 years in the MSH Drug Price Indicator Guide (Management Sciences for Health International Drug Price Indicator Guide 2011).<sup>164</sup> This guide provides data from 31 LMIC procurement organizations and nine non-profit suppliers. Prices are reduced to a standard price for a common dosage for each dosage form. Such data is used as the International Reference Price (IRP) for the WHO/HAI price and availability surveys.

### **4.2 Infrastructures outside Europe**

#### **4.2.1 High-income countries**

During the last fifteen years, the OECD has produced several works on how to promote innovation for medicines while increasing access to medicines. Major studies in this study were Pharmaceutical Policies in OECD Countries: Reconciling Social and Industrial Goals<sup>165</sup>, Survey of Pharmacoeconomic Assessment Activity in Eleven Countries<sup>2,27</sup> and the current study on value-based pricing.<sup>27</sup> As in Europe, there are groups and networks for sharing information and experiences in other areas as well. One of them is the Vancouver group, with Canada, Australia, New Zealand and some European countries being represented.

#### **4.2.2 Low- and middle-income countries**

In 2000, in response to global immunization rates stagnating, the Global Alliance for Vaccines and Immunization (GAVI) was launched to fund vaccines for children in the world's 70 poorest countries. Since then, GAVI support has resulted in the immunization of millions of children with different vaccines.<sup>166</sup> Based on a WHO resolution, the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) open to all Member States was established in 2006, with the aim to develop a global strategy and plan of action aimed at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect LMIC, proposing clear objectives and priorities for research and development, and estimating funding needs in this area. In May 2008, the World Health Assembly adopted the global strategy and the agreed parts of the plan of action on public health, innovation and intellectual property. To this end, the global strategy proposes that WHO should play a strategic and central role in the relationship between public health and innovation and intellectual property within its mandate.<sup>167</sup>

The WHO/HAI Working Group has developed a methodology to assess medicines' availability and medicines prices<sup>58,168</sup> which allowed building a database of survey findings<sup>169</sup> and performing valuable analyses. Gaps in the availability were shown for both acute and

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chronic conditions in the several LMIC, particularly in the public and private sector.<sup>61</sup> Overall, public and private sector medicines prices were shown to be substantially higher than “*would be expected if purchasing and distribution were efficient and mark-ups were reasonable*”.<sup>61</sup> Some analyses particularly focused on the price differences between originator and generics and showed that countries were overpaying.<sup>170</sup> Given the fact that most LMIC households have to pay out-of pocket for medicines, high medicines prices were shown to negatively impact affordability, and they have the potential to push large patients groups into poverty.<sup>171, 172</sup>

In 2010, the PAHO published a report investigating the situation on access to high cost medicines in the Americas and proposed strategies to improve the situation.<sup>173</sup>

Since 2008, the Netherlands-based Access to Medicines Foundation has published a biannual ranking of the top 20 research-based pharmaceutical companies based on their policies and performance to increase access in LMICs. Given that generic medicines make up some 80 per cent of the medicines sold in LMICs, a similar ranking for the major generic companies may prove useful.

### Networks and infrastructure: research priorities

- Evaluate and document the value added of research networks and EC initiatives
- Bridge the cooperation between regulatory authorities and pricing and reimbursement institutions
- Share data on relative efficacy (e.g. evidence tables)
- Support databases, information systems and networks for sharing price information

## 5. Conclusions

This background paper started with the notion that one of the major challenges in (inter)national policies regarding the pricing and reimbursement of medicines is how to align the necessity to control healthcare expenditures with creating sufficient incentives for innovations addressing public health needs. In most European countries, a variety of pricing and reimbursement policies have been implemented during the 1990s and 2000s, primarily in response to increasing pharmaceutical expenditures. Such policies included external price referencing, internal reference pricing, and the use of HTA and economic evaluation in reimbursement decisions. Yet, concerns over both the sustainability of healthcare costs, rewarding innovation, and cost containment continue to exist, prompting the question whether current policies are successful in achieving their intended goals.

The coming years therefore require a systematic and careful assessment and evaluation of the different tools and policies available, a refinement of methodologies, and an assessment of the impact on medicine use and pharmaceutical innovation. This will require significant investments and the involvement of stakeholders will be paramount in this process. Furthermore, it may result in the discovery of ‘uncomfortable truths’ and strongly diverging

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points of view of stakeholders will need to be accommodated. Simultaneously, the development and implementation of policies that will make for a truly sustainable and innovative European pharmaceutical sector in the long run are immense - for governments, companies, payers and patients – and therefore, an assessment and evaluation of tools and policies available is evidently needed.

We identified three key interlinked strategies that are available to regulators to control costs and reward innovation of medicines: managing price, managing volume, and managing which products will be reimbursed. Historically, policies have mainly focused on managing prices and managing reimbursement. In recent years two developments can be identified; first, it is increasingly being recognized that policies only serving a single policy goal such as cost-containment might not result in favorable long-term effects on innovation, and second, policies that impact *all* these factors (prices, reimbursement, and volume) might be most efficient in aligning conflicting policy aims. In line with these developments, HTA and value-based pricing have been identified as promising policies, but even though much research has been done in the field of economic evaluations, HTA, and pricing and reimbursement of medicines, a number of knowledge gaps remain. Further research is needed for the analysis of existing practices, for developing practical “tool boxes” and models for new approaches, and for studies that evaluate the introduction of new policies. In addition, this knowledge and (country-specific) experience should be appropriately communicated and disseminated, e.g. via networks for policy-makers.

European countries currently use a range of policy options that aim to control pharmaceutical expenditure, stimulate innovation, and ensure financial access to medicines. External price referencing is the predominant pricing policy in Europe and is increasingly being used outside of Europe as well. Payers are motivated to use external price referencing as a tool to contain prices of new on-patent medicines. Evidence for both intended effects (lower prices), as well as externalities of the policy, is mixed and sometimes contradictory. The impact of external price referencing on price levels throughout Member States, the distortion of the system due to confidential discounts and rebates, the availability of medicines in lower income countries, delays in market launch, and potential long-term effects on incentives to innovate should be studied.

Even though it is unlikely that external price referencing will be replaced completely by other pricing policies in the short-term, the feasibility of implementing alternative pricing strategies and their impacts on incentives for innovation should be studied. Value-based pricing, which is currently used by Sweden and will be implemented in the United Kingdom in 2014, has been argued to enable efficient pricing together with providing long-term incentives for innovation. Evidence at this point, however, remains scarce and mainly theoretical. Evaluation studies of countries that have implemented or are planning to implement value-based pricing therefore are warranted.

There is widespread evidence that list prices throughout Europe do not reflect actual prices and therefore erode the cost-saving potential of external price referencing. External price referencing therefore could benefit from increased transparency of medicines prices particularly tender price information which are not affected by discounts and rebates and the support of initiatives for exchanging price information. Simultaneously, this could be seen as an important reason to consider alternative pricing strategies since the policy does not seem to achieve its intended goals – and other pricing and reimbursement policies, including

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value-based pricing, might have the potential to send clear signals to industry on what innovations are expected and valued by payers. Furthermore, this would enable payers to set prices that reflect their own willingness to pay for innovation, instead of having to rely on prices set by other countries and the success of other countries to achieve fair prices.

Many European countries are moving towards the use of HTA and economic evaluations in the reimbursement of medicines. Payers that consistently apply decision-rules in reimbursement based on cost-effectiveness, as well as other determinants, in the assessment and appraisal of medicines could provide an important positive incentive for pharmaceutical innovation. Existing initiatives of cooperation and networks within Europe and beyond improve evidence-based and informed national pricing and reimbursement procedures. Therefore, a continuation and expansion of cooperation and exchange of experience is needed. Research networks include EUnetHTA, CAPR and PPRI with international organizations such as Health Alliance International (HAI), the WHO and the World Bank (especially for networks between the EU and low- and middle-income countries). Existing networks such as EUnetHTA and the PPRI network could also provide a basis for future networks (e.g. by adding a more explicit academic component), and make important contributions to the development of methodology, such as generalizability and transferability of economic evaluations.

Many stakeholders expect an increasing role of EUnetHTA in joint reimbursement assessment, although joint assessment solely considers relative effectiveness of pharmaceuticals. Improvements in the methodology of cost assessment - especially considering the issue of transferability of economic evaluations - are needed. Such improvements could contribute especially to the quality of the data that small countries frequently need to rely on.

Pharmacotherapy at the interface of the outpatient and hospital sectors can be improved. At the moment these sectors operate as separate worlds from a pricing and reimbursement perspective in many countries. Legal and organisational aspects need to be addressed in order to abolish the duality in the system and to remove existing incentives to stakeholders for transferring treatments and patients between the in- and outpatient sector as stakeholders should be incentivized to define the best point of care, including pharmacotherapy, from a *therapeutic* perspective. Research is needed to explore the possibility of the implementation of policies applicable to both sectors such as joint reimbursement lists and joint therapeutics committees. The introduction of policies to improve interface management should be accompanied by evaluations. Interface issues are of at least equal importance in low- and middle-income countries.

Differential pricing and separation of markets must be possible in Europe to reflect differences in ability to pay for medicines between countries, especially in light of the economic crisis that has severely affected a number of European countries. Policy options that would facilitate differential pricing need to be studied and developed. The development of differential pricing models is currently very challenging due to the complex EU policy environment and the interaction of parallel trade and external price referencing. The extent of the impact of external price referencing and parallel trade, in terms of availability of medicines and the affordability of medicines in EU countries, and the impact of such policy for all stakeholders, should therefore be evaluated.

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There is increased recognition for the fact that price is only one determinant of pharmaceutical expenditure and that effective policies should consider volume as well. It can be expected that in the coming years, new and more adaptive policies will be developed for high cost and high volume medicines, with an increasing role for managed-entry agreements and HTA for such medicines. Furthermore, effective generics promotion policies need to be investigated before effective interventions can be implemented, as many countries still could achieve substantial savings through high uptake of generics combined with policies that result in low generic prices, including tendering.

In addition, more adaptive approaches to pricing and reimbursement need to be developed in order to account for the increasing role of HTA and economic evaluations, as well as the expected increase of rare disease medicines and stratified medicines (see Background Paper 6.19 and 7.5). Whereas many countries now determine a medicine's price at a single point in time (usually at market entry), moving towards adaptive pricing would allow for managed-entry agreements, price-volume agreements, as well as the re-evaluation of prices when new indications are added for a marketed medicine. Particular attention might be required for high-cost medicines and new approaches such as joint procurement of countries and new integrative funding models might be warranted. In particular, research is needed regarding orphan medicines and their high costs, due to the low number of data generally available for informed decision-making. Furthermore, societal support for high prices, equity considerations, and potential cooperative structures in data collection for cost-effectiveness evidence should be investigated.

Pricing and reimbursement policies play a crucial role in stimulating the future development of medicines addressing unmet medical needs through creating appropriate incentives for innovation. Within Europe, pricing and reimbursement decision-making takes place at the national level and there is much variety in policies and practices. Notwithstanding, dialogue and cooperation between countries, institutions, and stakeholders is needed at both the political as well as the technical level in order to facilitate long-term positive impacts on innovation. Formalised cooperation structures between regulators involved in marketing authorization and competent authorization for pharmaceutical pricing and reimbursement could further aid the improvement of the current European policy landscape for pricing and reimbursement.

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### Annexes

#### Annex 8.3.1: High level initiatives by the European Commission

##### G10 Medicines

In 2000, the Pammolli report about competitiveness of medicines from a European perspective was published and raised a discussion about the actual competitiveness of the European Pharmaceutical Industry compared with that of the United States model. A major finding of the report was that the European industry has been losing competitiveness as compared to the USA: “As a whole, Europe is lagging behind in its ability to generate, organise, and sustain innovation processes”.<sup>174</sup> The authors analyzed the development of prices and market shares in the European countries and concluded that national European markets were not competitive enough, particularly in some countries where prices and market shares were found not to vary substantially after patents expire.

In response to this issue, the European Commission, represented by Commissioners Erkki Liikanen and David Byrne, created in 2001 the High Level Group on Innovation and the Provision of Medicines, then called G10 Medicines.

The G10 was charged with exploring different ways of enhancing the pharmaceutical industry's competitiveness in Europe, without affecting the satisfactory and affordable delivery of healthcare services to the population. Three broad areas of study were taken into account: innovation; provision of medicines to patients; market structure in Europe, competition and regulation.

After one year, in May 2002, the G10 group produced a final report for Commissioner President Prodi, containing fourteen recommendations. Under the heading of “Competition, Regulation, Access and Availability in Markets” major recommendations of the G10 report <sup>147</sup> were:

*Recommendation 3:* Respecting national competence, Member States should examine the scope for improving time taken between the granting of a marketing authorization and pricing and reimbursement decisions in full consistency with Community legislation. To do this with a view to securing greater uniformity and transparency between markets and rapid access of patients to medicines.

*Recommendation 4:* [...] Member States - facilitated by the Commission - explore ways of increasing generic penetration in individual markets (including generic prescribing and dispensing). Particular attention should be given to improved market mechanisms in full respect of public health considerations.

*Recommendation 6:* That the Commission and Member States should secure the principle that a Member State's authority to regulate prices in the EU should extend only to those medicines purchased by, or reimbursed by, the State. Full competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets.

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*Recommendation 7:* The Commission should organise a European reflection to explore how Member States can improve ways of sharing information and data requirements to achieve greater certainty and reliability for all stakeholders, even if the decisions they take may differ. The objective is to foster the development of health technology assessment (HTA), including clinical and cost effectiveness, in the Member States and the EU; to improve the value of HTA, to share national experiences and data while recognising that relative evaluation should remain a responsibility of Member States.

### High Level Pharmaceutical Forum

In July 2003, the European Commission adopted the Communication "A stronger European-based pharmaceutical industry for the benefit of the patient - a call for action" which outlines the Commission's proposals for advancing the G10 recommendations. A key action within pharmaceutical pricing and reimbursement proposed was to *"provide a forum for member states to generate and share information on common relative effectiveness issues in the context of pricing and reimbursement decisions."*<sup>139</sup>

In 2005, the Pharmaceutical Forum was set up as a three-year process. It focused its work on three main topics: information to patients on diseases and treatment options; pricing and reimbursement policies and relative effectiveness; for each of these topics a Working Group was set up. While the G-10 was composed of ten selected private and governmental health stakeholders in Europe, the Pharmaceutical Forum was a much broader process. It involved EU institutions, all EU Member States, industry, health care professionals, patients and insurance funds being represented in the Working Groups.

The Working Group on Pricing and Reimbursement confirmed in its "Guiding principles for good practices implementing a pricing and reimbursement policy"<sup>175</sup> that decisions on cost of healthcare and pharmaceuticals are a national responsibility and it stated that Member States aim to achieve three overall objectives of (1) optimal use of resources to maintain sustainable financing of healthcare, (2) access to medicines for patients and (3) reward for valuable innovation. With regard to the latter, the Working Group agreed on the following principles which should not be understood as binding rules:

- *Set expectations:* It was argued that through its pricing and reimbursement decisions, each Member State tends to grant incentives (e.g. a high price and reimbursement level, or good access to the market) for those new products that it really appreciates as bringing valuable improvements compared to the standard therapy. The importance to reflect what are and will be the desired additional benefits and to allocate resources accordingly was highlighted (additionally a paper on the value of innovative medicines was developed, see below).
- *Recognise innovation:* Companies were asked to be prepared to clearly prove this added value versus existing therapies, and authorities should be prepared to recognise proven incremental benefits that are estimated valuable and reward them appropriately (i.e. with incremental price-premiums or with measures allowing a higher utilisation). Pricing and reimbursement mechanisms, as well as utilisation guidelines, were asked to be in line with this and ensure a scaled recognition and reward. It should thus not be expected that incremental benefits would be rewarded with break-through premiums. Where added value versus existing therapies cannot be proven and recognised, timing of market

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entry of a new medicine should be taken into account as well as its effects on competition. Products coming to market soon after the first-in-class originator are the result of a parallel R&D process and should be rewarded in parallel to the first-in-class originator. Products entering the market significantly later should not get a similar reward.

- *Be consistent when giving reward.* Criteria for pricing and reimbursement need to be transparent, as requested by the Transparency Directive, and consistent over time. This gives the right signals to companies on what innovations are expected and valued.

In addition to the “Guiding principles for good practices implementing a pricing and reimbursement policy”, further documents are produced and agreed upon in the Working Group on Pricing and Reimbursement:

- “Ensuring availability to medicines in small national markets in Europe”<sup>176</sup>: to understand economic factors which determine supply and production, and bring forward some potential solutions to ensure availability of supply in small markets.
- “Improving access to orphan medicines for all affected EU citizens”<sup>177</sup>: to identify the main bottlenecks not only related to (1) development, but also to (2) assessment, to (3) pricing and reimbursement practices by companies and by national authorities and to (4) awareness raising, and to bring forward some ideas to ensure timely and equitable access for all EU citizens to orphan medicines.
- “Characterisation of the value of innovative medicines”<sup>178</sup>: a bottom-up exercise, based on discussions and collection of views from the relevant Member State authorities on how to recognise, assess and reward valuable innovative medicines, in order to identify some common ground between individual Member States.
- “From assessing innovative value of pharmaceuticals to pricing and reimbursement decisions”<sup>179</sup>: to clarify how some European Member States use assessments of innovative medicines in their pricing and reimbursement decisions.
- “The Toolbox exercise”<sup>28</sup>: to collect expertise from Member States and stakeholders for six selected practices (internal reference pricing, cost sharing, payback, prescription information, price control, generic substitution).
- “Risk-Sharing practices and Conditional Pricing of pharmaceuticals”<sup>180</sup>: to describe how these describes how these practices are set-up in different Member States.

In parallel to the Working Group of Pricing and Reimbursement, the Working Paper on Relative Effectiveness aimed to support Member States apply relative effectiveness systems in order to allow containment of pharmaceutical costs as well as a fair reward for innovation. In that working group, the following major documents were produced and agreed upon:

- “Core principles on relative effectiveness”,<sup>181</sup> which set out certain general principles of public administration that could be relevant for developing national systems and help to encourage of exchange of information, methodologies and experiences between the relevant national authorities;
- “Availability of data to conduct relative effectiveness assessments”,<sup>182</sup> which provided findings of provides a survey of the current processes on data availability during relative effectiveness assessments at national level; and
- “Development of networking and collaboration”,<sup>183</sup> which identified the most relevant networks and put forward recommendations for networking at the European level on this topic.

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### Platform on access to medicines in Europe under the Process on Corporate Responsibility in the field of Pharmaceuticals

Following on the G10 process and of the High Level Pharmaceutical Forum, the Process on Corporate Responsibility in the field of pharmaceuticals was launched in 2010 as voluntary multi-stakeholder process which aimed to find non-regulatory solution to several of the new challenges. The platform on access to medicines in Europe is one of its strands. Aiming at enhancing the collaboration among the Member States and relevant stakeholders in order to find common, non-regulatory approaches to timely and equitable access to medicines after their marketing authorization the Platform on access to medicines in Europe comprises six projects:

- *Mechanism of coordinated access to orphan medicinal products*: developing a concept of a coordinated access to orphan medicines based on the set up of programmes between companies and groups of competent authorities and results of the ongoing project on a mechanism for clinical added value on orphan medicines.<sup>184</sup>
- *Capacity building on managed entry agreements for innovative medicines*: to clarify the various approaches to managed entry agreements (also referred to as risk-sharing, outcome-based or performance based agreements) ensuring access to innovative medicines.<sup>185</sup>
- *Facilitating supply in small countries*: to clarify the specific non-regulatory bottlenecks for the access of medicines in small markets with all concerned parties with a view to defining possible specific approaches on pricing and reimbursement of medicines in these countries.<sup>186</sup>
- *Promoting a good governance for non-prescription medicines*: to identify the necessary elements to ensure informed and adequate uptake of medicines after a change of their classification from being subject to medical prescription to not subject to medical prescription.<sup>187</sup>
- *Market access for biosimilars*: to define what the necessary conditions within the pharmaceutical environment are to ensure informed, adequate uptake of biosimilars.<sup>188</sup>
- *Priority Medicines Report*: In order to ensure that the European Commission, Member States and relevant stakeholders are closely associated with the revision of the Priority Medicines Report 2013, the European Commission set up the "Prioritisation" working group under the umbrella of DG ENTR's Process on Corporate Responsibility in the Field of Pharmaceuticals. This working group is mandated to guide the revision process, and will serve as the advisory group to the project, i.e. give guidance as to the general directions of the whole project (including topics to be covered in the revised report).<sup>189</sup>

The outcomes of the five first working groups of Platform on Access to Medicines in Europe have been finalized and were endorsed by the Steering Group in April 2003.<sup>190</sup>

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### Annex 8.3.2: Price data of selected medicines (in Euros)

Country	Blood	Alimentary tract and metabolism		Nervous system			Antineoplastic and immunomodulating agents			Antiinfectives
	Prasugrel 10 mg/tab	Insulin lispro 100 u/ml inj 3ml	Pioglitazone 30 mg/tab	Naratriptan 2.5 mg/tab f/c	Galantamine 16 mg/cap MR	Aripiprazole 10 mg/tab	Bevacizumab 100 mg/4 ml inj	Mycophenolate mofetil 500 mg/tab	Sunitinib 12.5 mg/cap	Adefovir dipivoxil 10mg/tab
Austria	1.64	5.90	1.35	4.58	1.20	3.61	368.00	0.77	43.83	16.40
Belgium	1.60	5.80	1.15	1.48	1.57	3.68	323.08	0.97	43.38	11.23
Switzerland	2.22	8.48	1.47	5.07	2.73	5.25	429.76	1.79	59.01	20.21
Germany	2.19	8.94	1.30	1.38	1.59	6.49	364.78	1.45	50.51	17.75
Denmark	2.03	6.93	1.56	4.92	3.51	4.29	326.21	0.26	40.39	17.75
Spain	0.94	9.34	0.77	3.40	2.36	3.22	341.71	0.97	42.43	17.60
Greece	1.45	5.01	1.02	2.68	2.52	3.06	274.18	0.87	31.91	10.73
Finland	1.55	5.64	0.66	4.20	1.40	3.64	339.96	0.19	41.01	13.41
France	1.43	5.54	n.a.	1.43	0.68	3.10	295.88	0.94	43.81	16.60
Ireland	2.00	6.98	1.78	4.29	2.88	4.59	n.a.	1.85	43.64	11.57
Italy	1.56	6.35	1.22	n.a.	0.84	3.04	305.75	0.95	44.00	15.56
Netherlands	1.76	6.35	0.08	0.13	0.27	2.72	296.58	0.25	40.95	13.54
Norway	1.67	6.14	1.29	4.61	2.90	3.43	298.47	1.00	38.21	14.04
Portugal	1.48	5.46	0.55	1.49	1.02	2.66	361.90	0.81	42.50	n.a.
Sweden	1.89	6.58	1.21	4.73	2.92	4.71	350.51	1.09	46.14	18.16
United Kingdom	1.84	6.15	0.61	4.22	2.39	3.72	301.15	0.29	30.43	15.00

Ex-factory prices per unit in Euro are indicated as of June 2012

If alternative medicines were on the market, the prices of alternative medicines were taken

Source: Pharma Price Information (PPI) service of Gesundheit Österreich GmbH (GÖG) / Austrian Health Institute

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