WHO/HAI Project on Medicine Prices and Availability

Review Series on Pharmaceutical Pricing Policies and Interventions

Working Paper 1: External Reference Pricing

WHO/HAI Project on

Medicine Prices and Availability

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Pharmaceutical Pricing Policies and Interventions

Working Paper 1: External Reference Pricing

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Abbreviations

ATC	Anatomical, Therapeutic, Chemical classification system
BNF	British National Formulary
CEDD	Common European Drug Database
CIF	Cost, Insurance and Freight
EASP	*Escuela Andaluza de Salud Pública* – Andalusian School of Public Health
EMA	European Medicines Agency
ERP	External Reference Pricing
FOB	Free on Board
GCC	Gulf Cooperation Council
GÖG	*Gesundheit Österreich GmbH* (Austrian Institute of Health)
HAI	Health Action International
IPR	Intellectual Property Rights
IRP	Internal Reference Pricing
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PPRI	Pharmaceutical Pricing and Reimbursement Information
PRVP	*Precio de Referencia para Venta al Público* (reference price for sale to the public)
RP	Reference Pricing
TRIPS	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization

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Acknowledgements

WHO/HAI Pricing Policy Working Group

Foreword

WHO/HAI Project on Medicine Prices and Availability

Since 2001, the World Health Organization (WHO) and Health Action International (HAI) have been working in partnership to collect reliable evidence on medicine prices, availability, affordability and price components in low- and middle-income countries. To date over 80 medicine price and availability surveys have been completed or are underway using the WHO/HAI methodology, with results publicly available on the HAI website (www.haiweb.org/medicineprices). While this work continues to expand, the WHO/HAI project has evolved from supporting research to using the results to effect positive changes in related policies and interventions.

The results of the surveys confirm that substantial opportunities exist to increase availability, lower prices, and improve the affordability of medicines in all regions of the world and at all levels of economic development. However, it can be challenging to identify and prepare suitable lines of response.

At the request of national policy-makers, WHO/HAI and a group of international experts have developed guidance on various policies and interventions to increase medicine availability and make medicines more affordable, with a focus on low- and middle-income countries. This guidance takes the form of a series of in-depth reviews on pharmaceutical pricing policies (generics policies, external reference pricing, mark-up regulation, pharmacoeconomics and cost-plus pricing) and other related issues including the role of health insurance in the cost-effective use of medicines, encouraging competition, and sales taxes on medicines. The reviews are not meant to recommend one policy intervention over another, but rather provide guidance to policy-makers on the design and implementation of various policy approaches. For each review, a policy brief will be published that highlights key points from the review.

The results of the policy reviews show that relatively little has been published about the use of pharmaceutical pricing policies and interventions in low- and middle-income countries. Therefore, the review papers are published as working drafts, to be developed as more becomes known on the use of these interventions in low-and middle-income countries. We welcome information and comments that will strengthen these reviews (please forward them to Margaret Ewen, Health Action International email marg@haiweb.org).

WHO and HAI would like to thank the authors of the papers, the reviewers, and all the national contributors who provided information on the use of the interventions in their country. We are also grateful to the members of the Pricing Policy Working Group who have shaped this work.

We hope these papers will be a useful resource, and encourage national policy-makers to tackle the challenge of developing and implementing policies and strategies that ensure universal access to affordable medicines.

<table>
<tr><td>Dr Hans Hogerzeil</td><td>Dr Tim Reed</td></tr>
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<tr><td>Medicines Policy and Standards</td><td>Health Action International Global</td></tr>
<tr><td>World Health Organization</td><td>Amsterdam</td></tr>
<tr><td>Geneva</td><td></td></tr>
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Executive summary

The high price of medicines is a major concern for policy-makers, insurers and patients. High prices can make medicines unaffordable, compromising equitable access to them, and threaten the financial sustainability of public health systems. This applies especially to new high priced medicines which are protected by exclusive market rights, such as patents and data protection.

From the early seventies, most industrialized countries began creating mechanisms aimed at containing pharmaceutical costs in the face of rising prices and limited health service budgets. Price control is one of the oldest and still more widespread forms of pharmaceutical cost-containment, but even in the narrower context of direct product price control, there are a large number of modalities and variations in the way price regulation is designed and implemented.

In recent years, many countries have introduced the practice of External Reference Pricing (ERP), where the national regulated price is derived from or somehow related to those in a 'basket' of reference countries. ERP is defined in this paper 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". There are many modalities of ERP with varying combinations of methods for choosing or calculating external reference prices and also many ways to apply ERP in practice. Therefore, assessing the impact or merit of ERP, in relation to other pricing approaches, can be difficult.

A literature search revealed few published articles on ERP. Therefore, in order to gain a greater understanding of how ERP is applied in a variety of low and middle-income countries, a survey was undertaken in a sample of countries currently using this mechanism. The countries stated that they combine between two and five criteria to set prices along with ERP.

The use of ERP appears to be more justified for countries which have limited technical capacity or the resources required for more complex price regulation mechanisms such as pharmacoeconomic analysis. Countries need to consider the appropriateness of ERP along with all other options for attaining efficient medicine prices, including promoting price competition through the introduction of competitive policies – especially in the case of off-patent medicines – as well as other price regulation options. The application of ERP should be objective and transparent, in order to provide opportunities for assessing its effects, make decision-makers accountable, reduce uncertainty for the pharmaceutical industry, and diminish the risk of discrimination and corruption.

1.   Introduction

1.1   Pharmaceutical price regulation options: objectives and modalities

The high price of medicines is a major concern for many policy-makers, insurers and patients. High prices can make medicines unaffordable, compromising equitable access to them, and threaten the financial sustainability of public health systems. This applies especially to new expensive medicines which are protected by exclusive market rights, such as patents and data protection. These protections, which most developing countries have been obliged to adopt as a result of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and trade agreements, adversely affect access to medicines as they usually result in higher prices that consumers and insurers must pay.

The ultimate public health goal of pharmaceutical policy is to improve a population's health and wellbeing. This is best attained by low-priced medicines which consumers can afford. Publicly-funded medicine benefit programmes are also important in ensuring equitable access to medicines and the sustainability of such programmes depends on the negotiation of affordable prices.

There is a broad consensus that competitive forces are not usually present in pharmaceutical markets, at least to a sufficient extent to ensure efficient prices. Consequently, there is broad agreement that some form of intervention, either to effectively promote competition or to regulate prices, is needed. To the extent that intellectual property rights (IPR) confers a monopolistic position to the supplier, there is a fair theoretical justification for price regulation. In the early nineties, most industrialized countries began creating mechanisms aimed at containing pharmaceutical costs in the face of rising prices and limited health service budgets. Yet there is a surprising lack of agreement on the best types of intervention to apply. Direct product price control is one of the oldest and still more widespread forms of pharmaceutical cost-containment. It can be achieved through legislation (as in South Africa). But even in the narrower context of direct product price control, there are a large number of modalities and variations in the way price regulation is designed and implemented. One of the key elements is the way the regulated price is determined. In the past, most countries based the price on the cost of production with a profit margin plus supply chain charges (cost-plus method), or a comparison with the cost of similar existing treatments (internal reference pricing) to set prices. In recent years, many countries have introduced the practice of External Reference Pricing (ERP), where the national regulated price is based on a comparison with those in a 'basket' of reference countries.

An optimal price regulation system must have certain characteristics. First of all it should be in line with previously agreed policy objectives. Affordability, financial sustainability and assured product quality are probably the main objectives of price regulation. In that sense, price regulation should be directed at attaining lower prices than those that would otherwise prevail. But countries may also have other policy objectives such as improving innovation, availability

and domestic production and these objectives can conflict with the main policy aims noted above. At present, the price of medicines provides the main reward to the pharmaceutical industry in the form of extraordinary profits, i.e. profits higher than the normal profits that would be obtained under perfect competition. This is a key incentive for private innovators in research and development (R&D). For developing countries, the effect of price regulation on innovation is probably not a main concern, as they do not often have an innovative pharmaceutical industry. Moreover, innovation is usually led by global market trends and the impact of regulation in a single developing country on innovation is probably negligible. However, low prices 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. This outcome might deprive patients of effective treatments and negatively affect their health. But quick access to new medicines might also have some risks, as there is a higher likelihood of being affected by adverse effects that were not identified before market authorization.

A price regulation system should be easy and not too costly to administer. It should also be objective, transparent and predictable, meaning that there is limited room for regulators' discretion and all parties affected, particularly suppliers, are able to predict the price that will be granted and take their decisions accordingly. If the outcome of the regulation is difficult to predict, suppliers are forced to take decisions with a higher uncertainty, which in the end means they will be less likely to make certain investments. This is most relevant for R&D, but it also applies to other activities, such as manufacturing and registering products in a given country.

1.2   External reference pricing definition and characteristics

According to the Organisation for Economic Co-operation and Development (OECD), External Price Referencing, also referred to as External Price Benchmarking or International Reference Pricing, is defined as "the practice of comparing pharmaceutical prices across countries" and it is further indicated that, "There are various methods applied and different country baskets used" *(1)*. This definition was adopted by the European-funded project Pharmaceutical Pricing and Reimbursement Information –PPRI[a]- and for other pricing policies reports[b] *(2,3)* .

However such a definition seems too loose to characterise a pricing policy practice. Even if one accepts that ERP includes a continuum of approaches using various methods, the definition should at least mention the final purpose of ERP, i.e. to provide institutional purchasers and price regulators with a target, benchmark or reference price for setting or negotiating the price of a pharmaceutical product. García Mariñoso et al. state that "External referencing (ER) imposes a price cap for pharmaceuticals, based on prices of identical products in foreign countries", which they contrast with "directly negotiating the drug's price with the firm" *(4)*. Although this implicit definition recognises the final purpose of EPR mentioned above, it can be also criticised on the grounds that regulators might not always be able or willing to "impose" a certain price, but instead use the price computed as a benchmark or reference for negotiations, often alongside other criteria, such as cost-plus, internal or therapeutic pricing.

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[a] http://ppri.oebig.at/

[b] Vogler et al., PPRI Report, http://ppri.oebig.at Publications

The suggested definition of ERP for the present study is "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".

In this sense it is important to distinguish ERP from "internal reference pricing" (IRP), a widely extended pharmaceutical policy mechanism defined as the practice of using the price(s) of identical medicines (ATC 5 level) or similar products (ATC 4 level) or even with therapeutically equivalent treatment (not necessarily a medicine) in a country in order to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement of the product in a given country[a]. ERP should also be distinguished from "reference pricing" or "reference price system" where the third party payer determines a maximum price (= reference price) to be reimbursed for certain medicines. On buying a medicine for which a fixed price / amount (the so-called reimbursement price) has been determined, the insured person must pay the difference between the fixed price / amount and the actual pharmacy retail price of the medicine in question, in addition to any fixed co-payment or percentage co-payment rates. Usually the reference price is the same for all medicines in a given ATC 4 level and/or ATC 5 level group[b].

The methods for choosing or calculating the external reference prices can vary in several aspects. Factors to be considered are: the criteria used to choose the 'basket' of reference countries, including the adequacy of their medicine regulatory system; the number and specific set of countries used as references; the date of the price in the reference countries (e.g. current price vs. price at launch); and the selection or calculation of the reference price (lowest price in the set, simple average of all products, weighted average, etc). The resulting figure might be adjusted by a specific parameter to take into account the lower economic capacity of the country relative to the reference countries, for example. ERP can be used as the only criterion to inform the target price estimation, or can be one among several criteria such as cost-plus or internal reference pricing. These different values can be brought together as part of the deliberations of the decision-making body. The reference price can be enforced rigidly as a condition to either authorise the marketing of the product in the country, or (more commonly) as a condition for the health system's coverage and reimbursement. Alternatively it can be used as an explicit or undisclosed benchmark in a negotiation process.

In the case of ERP, predictability and transparency are required in the specification of the list of reference countries, the sources of data for the prices in the reference countries, the procedure to follow if the relevant price data is not available, the adjustments, if applicable, to account for confidential discounts or rebates in list prices or for differences in income levels, and so on. The description of the procedure for arriving at the RP should include, if applicable, the way other criteria besides ERP contribute to the calculation of the target or reference price.

1.3   Evidence of impact of external reference pricing

Assessing the impact or merit of ERP in relation to other pricing approaches is a difficult task. As controlled experimental designs are not likely to be feasible, the main approaches available are observational studies using either repeated cross-sectional studies or a time-series approach.

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[a] http://ppri.oebig.at/ *Glossary*: *Internal price referencing*

[b] http://ppri.oebig.at/ *Glossary*: *Reference price system*

In general, cross-sectional analysis is not the most appropriate tool to assess impacts and causal relationships. Moreover, comparisons across countries might be difficult because no two ERP systems are exactly the same. Longitudinal (time-series) analyses require repeated estimates covering a sufficiently long period before and after the introduction of ERP to provide stable estimates of changes in the measurement slopes. Ideally the analyses should include both intervention countries and controls, but this type of information is seldom available. In the absence of controls, the assessment requires modelling and some method of estimating the counterfactual, i.e. what would have happened if ERP had not been introduced. The latter always involves untested assumptions and a certain degree of subjectivity.

Whichever approach is used it may prove analytically impossible to separate the effect of ERP from the effects of other policies that are applied simultaneously. For example, how far can an observed delay in the launch of new medicines in a given country be attributed to ERP and not to parallel trade or low prices - three situations which often appear together? Moreover, it is often difficult to know to what extent ERP is actually influencing pricing or whether it is just an information gathering exercise with no real impact on actual prices. There is also some evidence that in some countries ERP is included in the legislation but not applied in practice.

Our literature searches uncovered few articles in scientific journals that dealt directly with ERP. There were some that examined price differences among countries. These studies mainly used the IMS Health database, comparing nine or ten countries, with the majority being from the OECD. Only one of those articles included a developing country (India) *(5)*.

Comparative analyses conducted using ex-manufacturer prices analyzed a variable number of pharmaceutical baskets, ranging from 15 to 249 medicines in different categories: high-sales generics *(5)*, biotechnology medicines *(6)*, or most frequently used medicines *(7)*. These articles show that after adjusting for GNP per capita, prices are higher in countries with lower income levels and regulated medicine prices (Spain, Portugal and Greece, for example) than in countries with high income levels (Japan, Germany and the UK) *(6, 7, 8)*.

Several difficulties and limitations must be taken into account when using ERP *(9, 10)*:

- Considerable resources (human and material) are needed to analyze the data.

- It may be difficult to identify the same medicine precisely due to different commercial names, dosage form, strength and packaging.

- Price comparisons are made much more complex because of the heterogeneous nature of distributors' profit margins, pharmacists, taxes, etc.

- Confidential agreements between manufacturers and purchasers often provide buyers with discounts or other benefits. If the results obtained from such negotiating processes are not transparent, it becomes harder to predict their impact in reference countries.

2.   Objectives

The objective of this paper is to describe, analyse and discuss the use and impact of external reference pricing, with a particular focus on low- and middle-income countries:

Objective 1:

To identify and characterize the use of External Reference Pricing and its impact on the price of pharmaceuticals.

Objective 2:

To describe the methodologies and impacts of External Reference Pricing on medicines, with a particular focus on low- and middle-income countries.

3.   Methodology

3.1   Structured literature review

A structured review of the literature was conducted. First, a search strategy was designed using Thesauri in two databases: *MEDLINE* (table 1) and *EconLit* (table 2). Then the search was completed by using key words and free terms in the following databases and websites: *Web of Science*, *EconLit*, *NHS EED*, *INRUD (International Network for the Rational Use of Drugs*), *La Biblioteca Cochrane Plus, International Political Science Abstracts*, OECD publications, WHO publications, The World Bank Documents and Reports, NBER (National Bureau of Economic Research, and Google Scholar. Finally, some documents referenced by experts have also been included.

Table 1. **Search strategy for MEDLINE**

Search	Terms Used	Results
#1	Search "Drug Costs"[MeSH] OR "Economics, Pharmaceutical"[MeSH]	10.549
#2	Search "Cost of Illness"[MeSH] AND "Cost of Illness"[MeSH]	11.395
#3	Search (#1) NOT (#2)	10.058
#4	Search "Pharmaceutical Preparations"[MeSH] AND ("Pharmaceutical Preparations"[MeSH] OR ("Pharmaceutical Preparations/economics"[MeSH] OR "Pharmaceutical Preparations/supply and distribution"[MeSH]))	433.537
#5	Search (#3) AND (#4)	1.411

Table 2. **Search Strategy for EconLit**

Terms	Results
(SU reference pricing) AND (SU drug or drugs or pharmaceuticals or medicines or medicament or medicaments or medication) AND ((TI international or external or benchmark) or (AB international or external or benchmark)) AND (AB "international" or AB "external" or AB "benchmark" or AB "bench marking" or AB "cross-country" or AB "cross country") AND (KW "pharmaceutical" or KW "medication" or KW "drugs" or KW "medicines" or KW "medicament" or KW "medicaments"). Limited 1990-2009.	86

The following key words or free terms were used: Topic = (Reference Price System) OR Topic = (International Referencing) OR Topic = (External Referencing) OR Topic = (Price benchmarking). For the selection of articles, all studies that mentioned external reference pricing were included - whether they were original articles or reviews - in the following languages: English, Italian, French, Spanish and German. The selection of articles was conducted in different phases. First, the title and summary for each article were read; only those that were clearly related to the research question were selected for inclusion. Upon completing that phase, the full text was read carefully by technical experts; articles that did not comply with the study's specific criteria were excluded. All articles were reviewed by two authors, which decided by consensus the final selection or exclusion. Next, EndNote software[a] was used to create a database of the selected articles and duplicates were excluded. Finally, a qualitative synthesis of the results was produced.

3.2   Search strategy
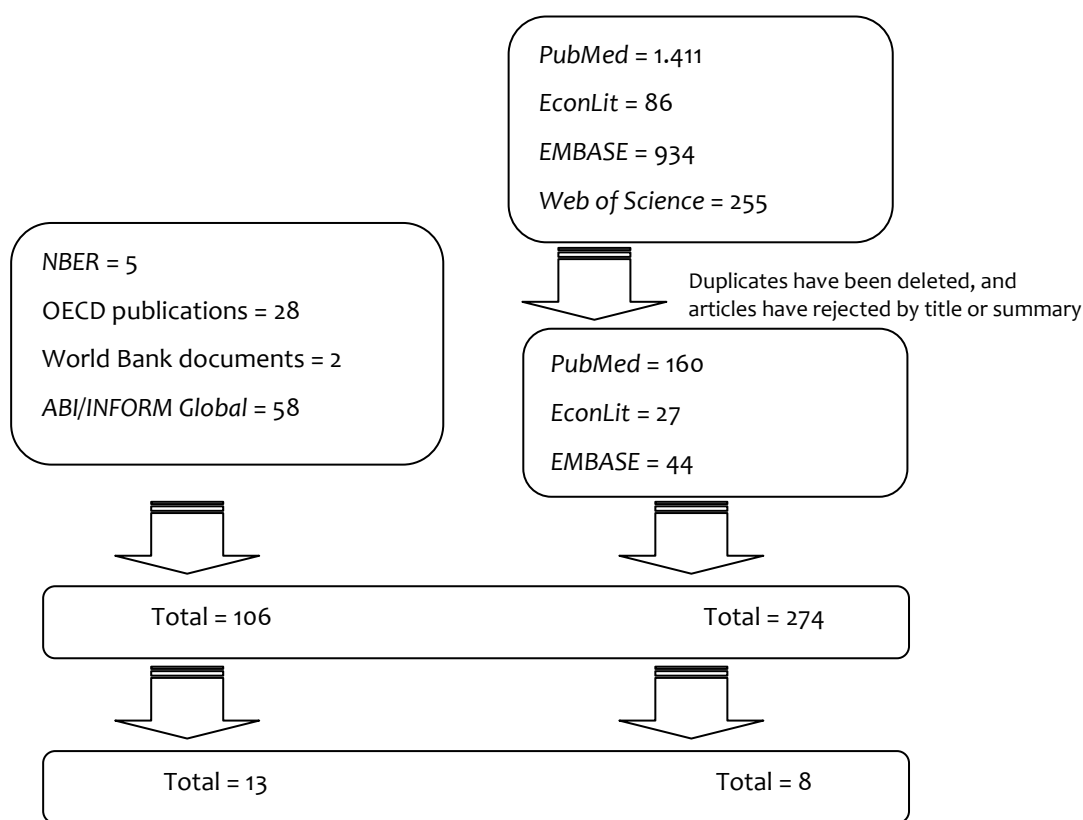
Figure. 1. **Flow chart of the document selection process**

A total of 2,686 bibliographic references were obtained from searches on the following databases: *MEDLINE*, *EMBASE*, *EconLit* and *Web of Science*. Duplicates, as well as articles whose titles and summaries did not conform to the search criteria, were eliminated. A total of 2,412 articles were excluded. While many of them addressed aspects related to setting medicine prices and pharmaceutical policies, the most common reason for excluding studies was because they did not address issues related to the use and impact of ERP. After a close reading of the full result, a total of eight articles were selected for inclusion.

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[a] http://www.endnoteweb.com/

Searches using the same inclusion criteria were conducted on other information sources such as the internet. Reports from a variety of sources were included and after eliminating duplicates the number of results was: OECD publications (3), World Bank documents (2), NBER (5), *ABI/INFORM Global* (58) and Google Scholar (7). Following a full text reading, 13 documents were retained. Finally, experts selected three documents for inclusion.

3.3   Country case studies

Between July and October 2009, a survey was carried out in a selection of countries that were currently using ERP in an attempt to obtain a varied representation of low and middle-income countries from all continents. Unfortunately reliable global information on which countries are using ERP as the single criterion or as one of the criteria for setting the price of medicines is not available. Several sources were used to identify the countries that could be used as case studies: the previous literature review, previous studies made by the authors and personal recommendations from experts. WHO and HAI carried out a quick and short survey (four questions) among low and middle-income countries in order to check which ones were using ERP. Finally, the following countries were selected: Brazil, Colombia, Czech Republic, Hungary, Indonesia, Iran, Jordan, Lebanon, Mexico, Oman, South Africa, United Arab Emirates and Yemen. Italy was included also in the selection because it was the only country known to have once applied ERP and discontinued it (in 2001).

A survey of 27 questions was designed[a] with 11 multiple choice questions and 16 open questions. Apart from this survey, four additional questions were specifically designed for Italy as an example of a country that has stopped using ERP[b]. A pilot test was done in July 2009 to a subgroup of 3 countries (Brazil, Czech Republic and Hungary) to assess the appropriateness and comprehensibility of the questionnaire, and two of them provided comments and suggestions that were incorporated in the final version. The questionnaire was designed in English and translated into Spanish for Mexico and Colombia. The next step was to contact those in charge of determining/negotiating the prices of medicines in the countries selected[c]. After explaining the objectives of the survey, the countries were invited to participate. The questionnaires were administered by email. In order to ensure a high response rate, several contacts were made (email and/or telephone call) with the officers in charge of answering the questionnaire.

The completed questionnaires were reviewed by two people in order to check that that the questions had been correctly understood and answered. In some cases the questionnaire was sent back to the respondents for clarification or doubts were cleared on a telephone call. Finally, a descriptive analysis of the results as well as a qualitative summary of the answers was carried out.

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[a] HAI, WHO and GÖG collaborated with the authors on the survey design.

[b] (1) Why external reference pricing is no longer used; (2) what is the new method and what is the impact of the change; (3) what lessons have been learnt; and (4) a detailed description of the external reference pricing methodology previously used.

[c] The WHO Regional Office for the Americas facilitated the contacts between the EASP and the national officers that could answer the questionnaire.

4.   Results

4.1   Results of the structured literature review

The review's first finding was that an unexpectedly low number of articles existed on the consequences, impact, scope and limitations of using ERP as a criterion to set medicine prices. The majority of these documents refer to OECD countries (*2*, *11*), particularly the EU-15[a]; very scarce information is available from low or middle- income countries.

Of the 21 articles, 13 (61.9%) were review or opinion articles, four (19.04%) employed a theoretical model, three (14.28%) used databases, and only one (4.76%) applied a questionnaire in different countries. Not only did the review find very few analytical and comparative studies, but also that there was very little published information available on the criteria and procedures involved where ERP was used to set medicine prices, such as how the countries of reference were selected or what formulas were applied to obtain a reference price.

The review revealed that European countries tend to select as reference countries those that share economic similarities or geographic proximity (*1*, *2*, *12*, *13*). However, many differences were found between countries regarding the methodology used. For instance, the number of countries or sources utilized varies considerably (*6-10*). It is worth noting that a majority of countries used either the average or the minimum price taken from the set of reference countries.

Japan is of particular interest as they use ERP to adjust medicine prices upwards or downwards in accordance with a formula. As a result, Japan's prices can vary between 150% above or 75% below the reference countries' prices (*14*).

Mexico uses the weighted average of the ex-factory prices with respect to the previous quarter in the six countries with bigger sales. The reference prices are reviewed annually and verified by an external auditor. The ERP determines the PRVP (*Precio de Referencia para Venta al Público*) or the reference price for sales to the public by means of the formula: PRVP=ERP x 1.72. The multiplication factor of 1.72 corresponds to what is typically considered the combined average wholesale and retail margins in Mexico. (*15*)

In Slovakia, pharmaceutical companies must provide information about the price of a medicine in the country of origin plus eight European countries (Austria, France, Germany, Italy, Spain, Czech Republic, Hungary and Poland) before introducing it into the market. This method can result in high prices in Slovakia because prices in the country of origin (e.g. Germany, Japan, UK, US) are normally quite high. There can be a delay in the pricing and/or reimbursement

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[a] EU15: Belgium, Germany, Greece, Spain, France, Ireland, Italy, Luxemburg, Netherlands, Austria, Portugal, Finland, Denmark, Sweden, United Kingdom.

decision while waiting for information about the prices in the neighbour countries (Czech Republic, Hungary and Poland), but delay rules are not explicit (*16*).

In Estonia, ERP is used for reimbursed originator and generic medicines, using the manufacturer price level. ERP may include all EU Member States, but examines explicitly the prices of three countries: Latvia, Lithuania and Hungary. Latvia and Lithuania were chosen because these are the closest neighbouring countries to Estonia with a similar economic situation, population structure and epidemiological status. Hungary was chosen because it has a similar pricing procedure (negotiations with manufacturers) to Estonia (*17*).

The study by Garcia-Mariñoso *et al* (*4*) identifies two policies where ERP is used in conjunction with price negotiations with pharmaceutical companies:

- *Non-conditional ER policy* where one country uses another country's price as a reference for its own maximum, regardless of whether or not the other country's negotiations were successful.

- *Conditional ER policy,* where use of ERP depends on the other country having included the product in its list of subsidized medicines.

By employing different analytical models this study concluded that countries should use a variety of instruments to set their prices. It suggests that other countries' prices should only be used to set maximum prices when the medicine has been included in the reference country's positive list.

The literature often refers to the apparent consequences stemming from the use of ERP. Some studies conclude that ERP, together with parallel trade, can lead to the delay of a product's launch[a] in a country (*8*, *15*, *16*, *17*). Following an analysis of data from the *IMS Health* database, several studies detect a considerable variation between the number of medicines available and the average delay in launching of these medicines in the countries studied (*8*, *16*, *17, 18*). They conclude that countries with lower prices or lower market volume had fewer medicines available and also suffered from longer delays in medicine launches (once adjusted for other variables[b,c,d]). The alleged reason is that pharmaceutical companies have an interest in delaying product launches in low-price countries until the medicine has been approved for use in high-price countries, thus enabling them to keep prices high in the former.

One study cites examples from Germany and New Zealand, where some pharmaceutical companies decided to keep prices high for certain medicines (atorvastatin and ACE inhibitors) despite internal reference prices being lower, and a subsequent loss in market share. Companies knew that prices in these countries would later become references for other countries, and that those prices, in turn, would be used in other countries as a reference in the future (*18-21*). By

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[a] The delay of a product's launch is defined here as the number of months that elapse between the product's global launch and its launch in a specific country (with no distinction made between delays in obtaining the marketing authorization, delays in price setting/reimbursement decisions and the manufacturer's decision on when to launch).

[b] Danzon et al, 2005: Controlling for product, company, and country-specific factors, including income per capita.

[c] Kyle et al, 2008: Controlling for country–drug fixed effects and (2) interacting a dummy variable equal to 1 for European Union countries with dummy variables for each year in the data set.

[d] Danzon and Furukawa, 2008: Controlling for expected price and volume and per capita income.

keeping prices high in these two countries, the industry was able to obtain higher prices in other countries. Thus it seems logical to conclude that one consequence of ERP is that it puts pressure on countries that are selected by others as a reference country to keep prices high, especially if they want an early market entry of new products. A study conducted by Stargardt and Schreyogg (*22*) is relevant here. Using an analytical model they estimated that a €1 reduction in German medicine prices would lead to a reduction of between €0.15 and €0.36 in the EU-15 countries that use ERP (Austria and Italy, respectively).

ERP can become an incentive for pharmaceutical companies to adopt international pricing strategies that could eventually have negative impacts on prices within individual countries and unexpected consequences for countries applying such policies. The main alleged negative effects include: 1) higher prices in low-income countries that, in the absence of ERP policies, might benefit from lower prices, and 2) delays in the launching of new medicines in countries with low-priced medicines. This was made evident in a recent European Commission report that asked companies to indicate which countries they preferred to use for launching new medicines. Companies preferred to initiate their product launches in countries with free prices (United Kingdom, Germany, and Sweden). In contrast, countries with smaller markets, such as Cyprus or Malta, or with lower disposable income, such as Poland, Bulgaria, Lithuania, Latvia, Estonia, Hungary and Romania (*23*), are mentioned last. Considering the relatively small number of new medicines that actually make any substantial therapeutic contribution over existing ones, such delays in marketing might not necessarily be a bad thing.

4.2   Results of country case studies

A total of nine questionnaires were received (response rate: 69%)[a]. In addition Italy completed an additional short survey following their move from use of ERP to a negotiation procedure, which takes into account cost-effectiveness, market share and prices in other countries.

Table 3 summarises all the relevant information on the use of ERP in the selected country case studies.

The countries stated that they combine between two and five criteria to set prices. The second most used method is the cost of existing treatment for the same condition or disease within the same country (8 countries).

All countries mentioned the existence of an official document where the procedure for ERP is established. The average number of countries used as reference was 7.75 (range 4-8 countries); the most frequent justifications for the selection of the countries were that: 1) they are in the same region (55.5%), 2) the products have usually received marketing authorization in these countries when the price information is searched (33.3%), and 3) the availability of price information (22.2%). Some countries use as the comparator the manufacturer's country of origin (as in the case of Iran and Jordan). However, there are some countries that are commonly used as reference despite not necessarily being in the same region. Examples are Spain, France, and

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[a] There is only one country, Italy, where ERP was once introduced and later abandoned. In a previous study (*2*), it was stated that Italy used external reference pricing until 2001, taking into consideration the prices of Spain, France, UK and Germany. Then because of its apparent ineffectiveness in containing pharmaceutical expenditure, the system was abandoned.

the United Kingdom, which are chosen due to their low prices, transparency and accessibility of price information. A little more than half of the respondents affirmed their use of some international databases and websites as information sources, for instance the BNF (British National Formulary), CEDD, and *VIDAL Drug Compendium.*

In all of the case study countries, a manufacturer submitting a new product for pricing is obliged to provide the price of the product in the reference countries. Failure to do so or to provide false information could lead to fines and penalties.

Regarding the methodology for arriving at the reference price, the most widespread criterion was the minimum price of the set of reference countries (6 countries), followed by the average price (2 countries).

4.3   Summary of the country case studies

The more relevant results are:

- Some common elements across countries using ERP are:
  - ➢ The price used as reference is usually the ex-factory or manufacturer`s selling price.
  - ➢ The selection criterion for the basket of countries is the minimum price across the selected countries.
- Most of the surveyed countries use ERP for all products, the exceptions being Brazil, which applies it only to on-patent products, and the Czech Republic, which restricts ERP to publicly reimbursable medicines. Iran states that ERP is used only for imported medicines, which in practice are likely to be predominantly on-patent medicines.
- The countries used as reference are usually selected from within the region and with similar income levels. However, there are some countries (i.e., Spain, France, and the United Kingdom) that are often used as reference by countries from other regions. The reasons given are either relatively low prices or availability of information.
- The main sources of information are manufacturer's certificates and websites of the reference countries, and (only very occasionally), international price databases.
- Some countries claim to expect price decreases, but this claim is seldom supported by empirical evidence.

Table 3. **Summary table of key case study results**

| Country	Price setting	Products - ERP	Countries	Price used	Criteria	Sources of information
Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	On patent (Category I)	USA, Canada, Portugal, Spain, France, Italy, Greece, New Zealand and Australia	Ex-factory	Minimum	Websites;
Czech Republic	SUKL(State Institute for Drug Control)- maximum prices/reimbursement prices/ Health funds - price negotiations	Reimbursable	For pricing: Estonia, France, Italy, Lithuania, Hungary, Portugal, Greece, and Spain For reimbursement: all EU countries	Ex-factory	Average	Websites; Manufacturer
Hungary	National Health Insurance Fund Administration (OEP)	Reimbursable (new active substances)	Countries in the European Union and European Economic Area	Ex-factory	Minimum	Websites; Manufacturer
Iran	Pricing Commission	On-patent and imported	Greece, Spain, Turkey and the country of origin	Ex-factory and wholesaler	Minimum	Manufacturer
Jordan	Pricing committee of the Jordan Food and Drug Administration (FJDA)	All products	Selected European countries (UK, France, Spain, Italy, Belgium, Greece and the Netherlands), the export price to Kingdom of Saudi Arabia, and the country of origin	Ex-factory price of the reimbursed price	Median	Websites; Manufacturer
Lebanon	Pricing Committee - MoH	On- and off-patent products	Region: Jordan, Kingdom of Saudi Arabia, Kuwait, Sultanate of Oman, United Arab Emirates, Bahrain and Qatar. Comparative: France, England, Belgium, Switzerland, Italy, Spain and Portugal	All	Minimum	Manufacturer
South Africa	Pharmaceutical Economic Evaluations (PEE) Directorate	On- and off-patent products	Australia, New Zealand, Spain, and Canada	Ex-factory and import	Minimum	Manufacturer
Sultanate of Oman	Directorate General of Pharmaceutical Affairs & Drugs Control	All products	Gulf Cooperation Council (GCC) countries: Kingdom of Saudi Arabia, United Arab Emirates, Bahrain, Kuwait, and Qatar	Import price CIF (cost, insurance & freight)	Minimum	Manufacturer
United Arab Emirates	Committee - MoH	All products (some exceptions)	Country of origin and Gulf Cooperation Council (GCC) countries: Kingdom of Saudi Arabia, Kuwait, Bahrain, Qatar, and the Sultanate of Oman	Ex-factory and import	Minimum	Websites; Manufacturer
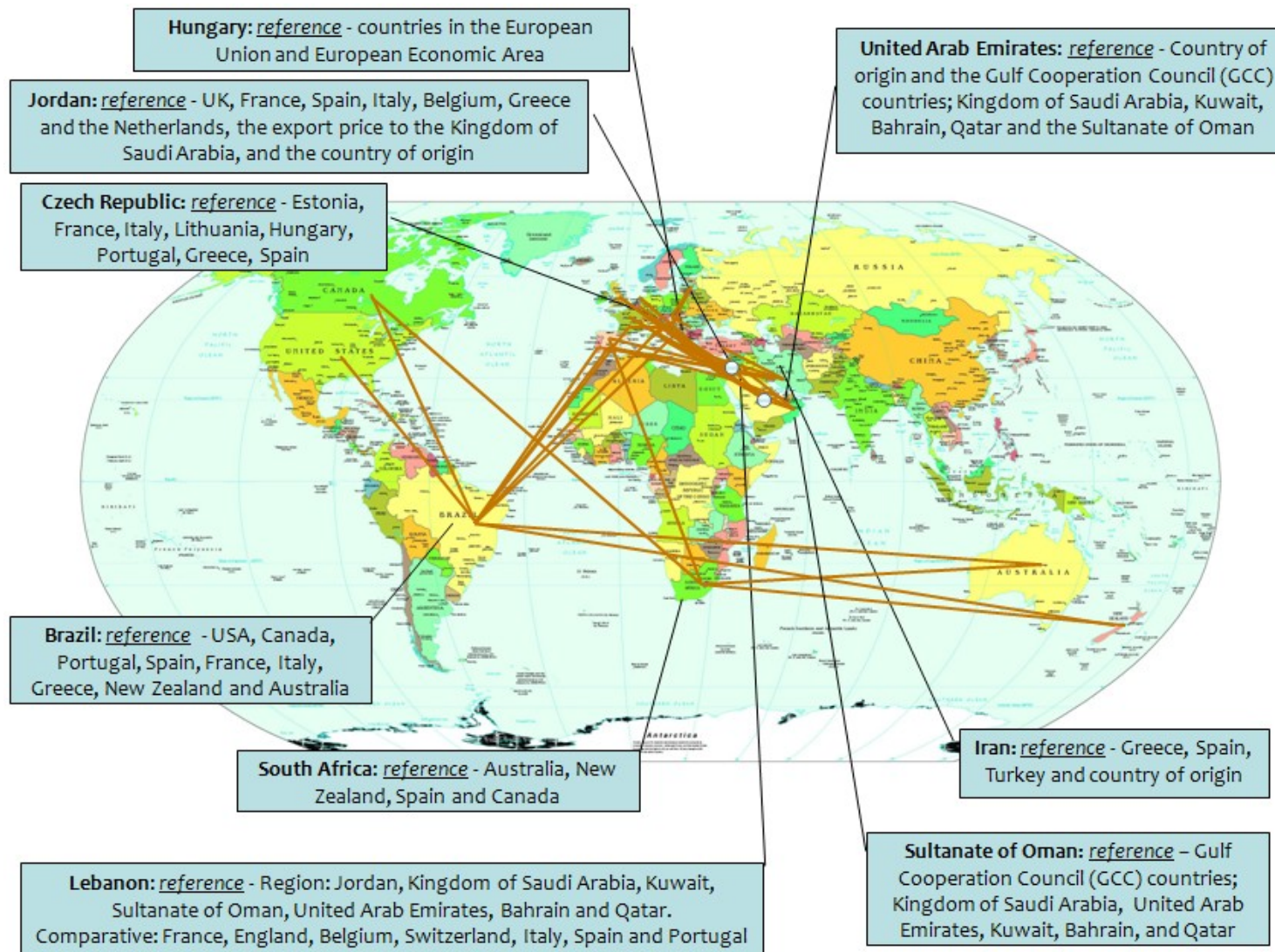
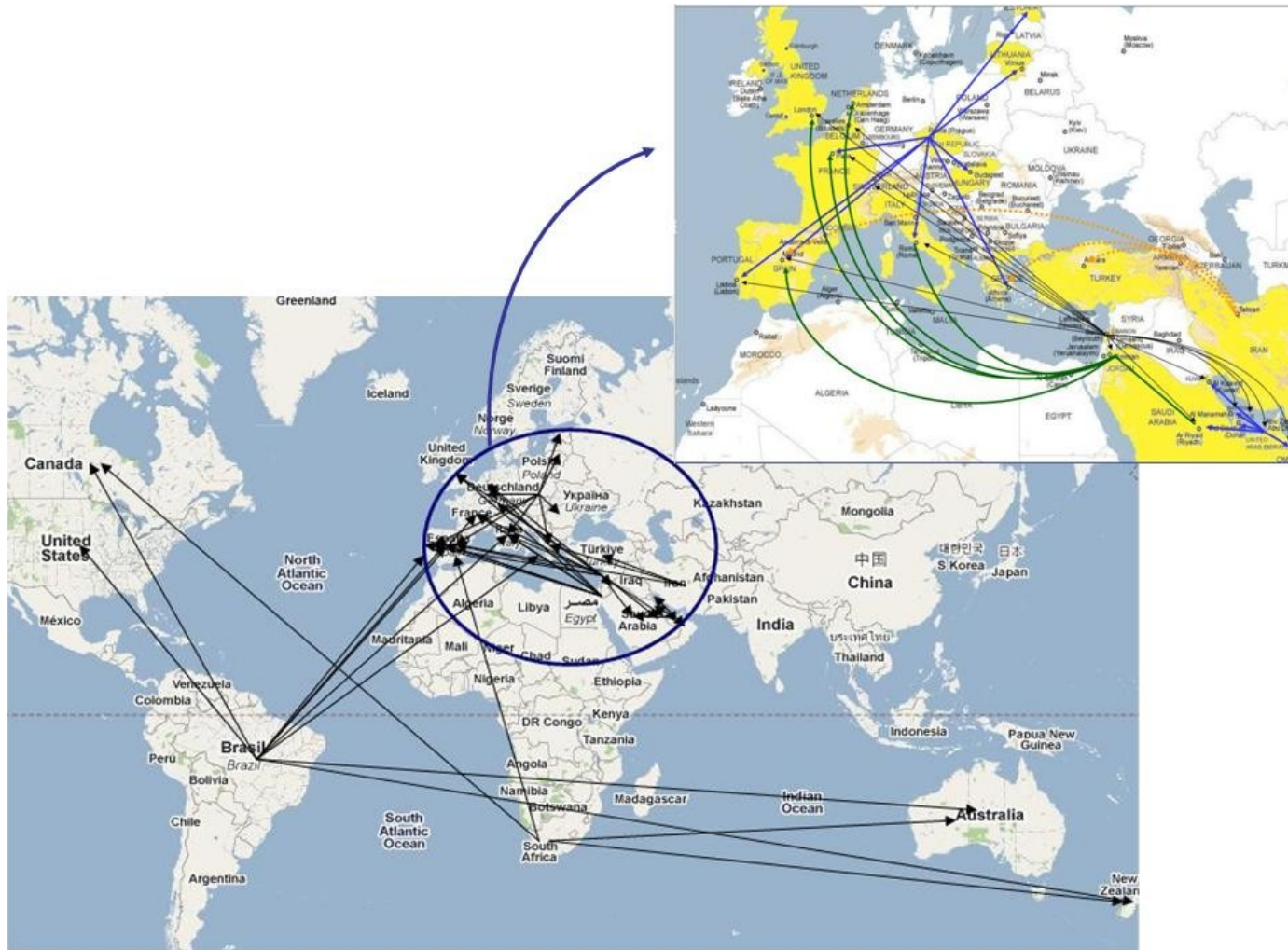Figure 2. **ERP in the selected countries used in the study**

Figure 3. **ERP in the selected countries used in the study (European countries in detail)**

5. Discussion

5.1 Where and how is external reference pricing used?

The use of ERP as a mechanism to set pharmaceutical prices is quite widely applied: 24 of the 30 OECD countries and approximately 20 of the 27 EU Member States use it. The case studies indicate that it is also becoming popular among developing and transitional countries. But despite a widespread increase in its use, information on how countries actually implement ERP is limited and few analytical studies have attempted to assess the intended or unintended effects of this policy practice.

Many variations exist in how ERP is applied including the number and characteristics of the reference countries and the formula or procedure for deriving the national price from the prices in the reference countries. Some countries have very detailed legislation and well-defined procedures on how to apply ERP that take into account possible situations that might arise (for instance, what to do if differences exist between the national market and the reference countries regarding the strength and pack, or what happens when the prices in some reference countries are not available at the time they are required), but in other countries such details are not established or not publicly available.

Developed countries usually restrict the use of ERP to on-patent medicines. However, most of the developing countries included in this study apply ERP to both on-patent and off-patent medicines.

Some countries use ERP as the single criterion to determine the prices of all medicines or some categories of medicines, while others use ERP as just one in a battery of approaches for pricing each single medicine of a certain type. Countries differ, as well, in how they enforce the calculated price: some present suppliers with a "take it or leave it" decision, meaning that if they do not accept the price offered, the product will not be approved or reimbursed. At the other extreme are some countries that use the calculated price as a relatively flexible benchmark for negotiating the price.

5.2 What are the effects of using external reference pricing?

There are a number of alleged consequences of using ERP. As has been extensively mentioned in the literature, some evidence points to market launch delays in low-price countries. Secondly, ERP might produce convergence in international pricing because companies could try to impose a single price worldwide and be unwilling to offer lower prices to any country, especially those that are, or might be, used as a reference by other countries. Consequently, countries that in the past were able to obtain relatively lower prices might not be able to do so in the future. Although the literature provides some evidence on the convergence of international prices of new medicines and marketing delays in low-price countries, it is difficult to assess how far this phenomenon may be due to ERP, parallel trade, or that these markets are less attractive to suppliers - a set of factors that are often simultaneously present in some countries.

The effects of ERP depend on the number and characteristics of the reference countries, how the national price is calculated or derived from the prices of the reference countries (minimum price, average, median), and whether the reference price is used as the actual national price or used as a relatively flexible benchmark. Answers to the questionnaires and previous experience of the authors suggest that the reference price does not often become the actual national price, especially in the case of medicines that enjoy a monopolistic position.

Some countries claim that the use of ERP has had positive effects in reducing the price of medicines (as much as 30%, in some cases), but no evidence from monitoring reports or rigorous analytical studies supports these claims. On the other hand, countries seldom consider potential long-term effects, such as delays in new product launches.

5.3   Is external reference pricing an appropriate price regulation mechanism?

In principle, ERP should be assessed in relation to the objectives of universal medicine availability, affordability, equitable access and the rational use of medicines[a]. However, it must be acknowledged that certain countries' actual objectives may diverge from these. A country might only regulate prices to reduce their pharmaceutical expenditure or to protect domestic industry. While most countries seem to use ERP to achieve lowest possible prices for medicines, others consider different goals. An example is Canada, which references to countries with large health research-bases (for example the UK, Switzerland, Sweden). This can be interpreted as recognizing investment in research and development in their pricing process.

A price regulation mechanism can be judged by several criteria. The first one should probably be its effectiveness, i.e. its capacity to attain the desired prices. It should also be feasible and affordable in relation to the technical capacities and resources of the country. Another aspect to be considered is whether the mechanism is objective – non discretional – predictable and transparent, as this reduces unnecessary uncertainty to the suppliers. This potentially leads to lower supply prices and fewer delays in marketing a product. Objectivity and transparency are also requisites for ensuring regulators' accountability and for reducing the risk of corruption and discrimination against certain suppliers. Finally, price regulation mechanisms should take into account the unexpected, long-term effects on the country itself as well as on other countries.

Although this paper focuses on ERP, it or any other policy option cannot be assessed meaningfully in isolatation. It needs to be considered by countries as one of a variety of pricing tools that can be implemented to attain the objectives of universal availability, affordable medicines, equitable access and rational use.

Compared to other price control mechanisms such as cost-plus or pharmacoeconomic analysis, ERP is a relatively simple method for countries to use because it does not require large amounts of information or an extensive technical/analytical capacity.

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[a] The promotion of socially needed innovations is implicit in these objectives as without innovation the future availability of medicines that improve existing therapies and cover previously unmet needs would be threatened

One of ERP main shortcomings is the lack of a clear rationale or theoretical foundation. For example, price control based on the cost-plus (or cost of production) criterion seeks to determine a price that allows producers to recover production costs and obtain a fair/acceptable profit. Pharmacoeconomic analysis assumes that the price of a medicine should reflect its therapeutic or welfare-added value in relation to existing therapies. It also assumes that new products that do not bring any added value should not get a higher price than existing treatments.

Although ERP does not have any clear rationale or theoretical foundation, the implicit assumption is that it reflects some of the following aims:

1. To obtain prices similar to – in fact, not higher than - those of a set of countries.

2. To obtain the same price as the lowest price in a set of countries.

3. To obtain differential - usually lower - prices in relation to those of a set of countries.

In any case, the underlying assumption justifying the use of ERP is that the prices in the countries taken as a reference are somehow right, appropriate or fair. All the method tries to ensure is that the country does not pay more than other countries do or that it pays less, because the country is not that wealthy. In that sense, ERP has some "common sense" appeal: it enables a country not to have to pay a much higher, unfair price, than a group of reference countries, usually neighbouring or similar-income countries.

In fact, when countries use ERP to set prices they are ultimately allowing other countries' pricing policies to determine their own by including approaches obtained from other countries' sets of reference. It is, however, difficult to assess whether the resulting prices will be appropriate, efficient or optimal in accordance with any objective criterion. If reference countries have set their prices too high or too low, then any country later applying the ERP method may run the risk of repeating the same mistake.

Obviously not all countries can rely on ERP. At least one country in the world should use a different method otherwise new products would never be priced and marketed. Currently this does not appear to be a problem, since some countries choose not to apply any form of price regulation, and among those that do, not all apply ERP.

5.4   What are the indirect effects of using external reference pricing?

An important issue to consider in relation to ERP is whether it has any unintended effects beyond its immediate impact on medicine prices, particularly negative effects on various stakeholders in the country applying it or on other countries. In analysing the effects of ERP as well as other forms of price regulation, two perspectives must be considered: the individual countries' perspective and the global perspective.

Medicine regulatory policies are usually a national responsibility, although there are clear trends towards globalisation of some aspects, particularly on efficacy and safety standards for market authorisation and intellectual property rights. The pharmaceutical market's globalisation, however,

spreads the effects of national price and reimbursement regulations well beyond the regulating country's own national boundaries.

Some of the potential effects might be the result of strategies adopted by the affected stakeholders, mainly pharmaceutical companies, in response to new conditions created by the widespread use of ERP. When a large number of countries began using ERP, companies became aware of spillovers – international effects – that stemmed from prices that were being set in a given country. They reacted by designing and implementing appropriate international pricing and marketing strategies to counteract the effects of ERP and maximise companies' global profits under the new conditions. These strategies might affect not only the countries that apply ERP, but others as well, especially those used as reference countries.

The main strategies adopted by companies are:

1. Trying to set a single international price for a product.

2. Delaying the launch of new products in countries that try to attain lowest prices, or even not market, especially in small markets where the opportunity cost of the strategy is lower, and countries that are referenced by other countries with larger markets.

3. Reducing price transparency in order to minimise the likelihood of spillover effects caused by international price differences

In the absence of ERP and parallel trade – i.e. when national markets are independent - companies could maximise global profits by trying to obtain the highest possible price in each single market, disregarding price differences among countries. This pricing strategy, known as discriminant monopolist, can be used only when there is one sole supplier of a medicine. Under present conditions – ERP and parallel trade – accepting different prices for the same product in different countries could eventually lead to the lowest price prevailing in all markets. But as companies seek to maximise global profits, wherever possible they could charge a higher single price for the same product in all countries. However, this single price might mean consumers in lower-income countries could not afford to buy the medicine.

Imposing a single international price is not a profit-maximising option compared to price discrimination and might not be feasible, anyway. Companies may, therefore, try to apply a second strategy: initially marketing a new product in countries where prices are not regulated or where high prices are common. Launches in lower-price countries may be delayed so as not to influence other countries. This company strategy will not work if the high-price country revises its prices downwards after launch.

Companies can reduce price transparency in many different ways. They can list high prices in reference countries while granting confidential rebates or discounts to them[a]; i.e. offering a discount or rebate under the condition that it will not be publicised. Companies might also provide a larger number of units than those indicated in the contract in exchange for maintaining the list price. These strategies provide manufacturers with a degree of flexibility in satisfying requests for lower prices from country regulators and payers without compromising prices in other countries that take the former as a reference.

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[a] In Germany, confidential discounts between insurers and pharmaceutical companies are very common.

As a result of these strategies, the objectives of countries using ERP may be hindered and the country might end up paying higher prices than intended. Smaller, lower-income countries might end up paying higher transaction prices than the higher income countries taken as reference.

ERP is not only distorted by the previously mentioned strategies used by pharmaceutical companies, but also by national or regional policies and regulations that affect the final price. Some examples are:

1. The use of pay-back[a] as a mechanism through which companies agree to return revenue over a predetermined level to public institutions in the form of annual lump-sums.

2. The general discount system used in countries such as Spain (one of the most referenced country) whereby manufacturers have to return 1, 2, or 3% of their annual sales to the Ministry of Health.

3. The profit control system in the UK, whereby a manufacturer sets the price freely but if profit margins from sales of branded medicines to the National Health Service (NHS) exceed the level granted to the company according to predefined criteria (mainly, involvement in research activities) they have the option of a payback or reducing the price the following year

4. Other risk-sharing agreements, for example, the UK's NHS is not required to pay for Velcade (bortezomib) if it is not effective ("outcome guarantee" agreement), but the listed price applies when the medicine works for 100% of the patients taking it.

These practices are not directly attributable to ERP, but are certainly more likely to be agreed and accepted as cost-containment policies by the pharmaceutical industry since they only affect the country concerned and do not have spillover effects on other countries.

How important are these indirect negative effects for the countries concerned? Price convergence is likely to be a serious problem for countries that experience higher relative prices as a result of ERP, especially if they are low-income countries, since this might severely affect affordability and the financial sustainability of the health system.

Regarding marketing delays, the loss of benefits depend on the added value of the medicines concerned. For medicines that make no therapeutic or economic contribution to existing treatments, a delay in launching, or even no launching at all, poses no real loss. Of course, some patients might forgo potential benefits from new medicines. But taking into account that "new" medicines do not always provide clear therapeutic advantages, and adverse effects are more likely to appear in the first years of the product life cycle, it is far from obvious that an early launch brings more benefits than costs to a certain country.

The loss of price transparency is probably one of the most undesirable effects of ERP. Prices represent the market's key mechanism for the efficient allocation of resources. Without known prices, markets simply cannot adjust to an efficient equilibrium. Collective decision making cannot be efficient either, since the underlying comparisons of costs and benefits will be biased or completely unfeasible. The ERP mechanism itself becomes distorted and can cause results different from those initially intended: decisions are made that are based on higher virtual prices rather than on actual transaction prices, i.e.

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[a] Pay-back is a risk-sharing mechanism that requires companies (either individually or collectively, e.g. via their industry association) to return a certain part of their "excess" revenue to a purchaser if sales exceed a previously determined target. This mechanism is used in Hungary, France, Italy, etc.

opportunity costs. Last but not least, price confidentiality eliminates (or at least reduces) accountability. Decision-makers involved in activities such as procurement and medicine regulation are less able to exercise institutional and democratic control, thus increasing opportunities for discrimination and corruption.

Summarizing the pros and cons of ERP, the main apparent advantages are:

- It is a relatively simple and easy-to-apply system compared, for example, to economic evaluation. Its implementation is feasible when resources are relatively limited, and it provides quick information to regulators and other policy-makers. This might justify its use by small countries with limited capacity to implement alternative pricing mechanisms. These countries should probably be more concerned about not paying too high a price than on the effects their pricing decisions might have on the global pharmaceutical market.

Some of the main limitations and apparent disadvantages are:

- Price information is not always available. Available prices are often heterogeneous (ex-factory, reimbursement, retail prices, etc.) and it is not always easy to adjust them to obtain the required type of price.

- It is difficult to find transaction prices; the prices that countries have access to are often not real prices, but virtual list/catalogue prices.

- Although there is no conclusive evidence about the impact of this practice, launch delays and the non-availability of new medicines in low-price countries may be a likely effect. Price convergence, resulting from higher prices in lower-income countries, and decreasing price transparency, are possible additional negative effects.

6. Recommendations

6.1 General considerations

Those considering the introduction of ERP can acquire fairly comprehensive information on the different types of ERP systems applied in other countries and their potential positive and negative effects. However, in the authors experience, it is more difficult to obtain detailed information on how such mechanisms are managed on a practical day-to-day basis and even more so on the indirect effects they have in their own and other countries over the medium- and long-term.

Most of the alleged effects of ERP are not supported by any rigorous evaluative research that demonstrates whether this apparently easy-to-apply system is effective in setting a fair, efficient and sustainable price structure. Taking into account the spillover effects of ERP and the fact that small, low-income countries might be the ones to experience the most negative effects of an increasingly widespread use of ERP, international organisations and research funds should ensure that empirical research is conducted so that future decisions on ERP design, implementation and use can be based on better evidence.

Countries must consider the appropriateness of ERP by taking into account all the alternative options for attaining efficient medicine prices, including promoting price competition through the introduction of competitive policies – especially in the case of off-patent medicines – as well as other price regulation options.

The use of ERP appears to be more justified for small, low-income countries, which might not have the technical capacity or the resources required for more complex price regulation mechanisms, such as pharmaceconomics.

The application of ERP should be as objective and transparent as possible, in order to provide opportunities for assessing its effects, make decision-makers accountable, reduce uncertainty to the pharmaceutical industry, and diminish the risk of discrimination and corruption.

Given the global effects of national ERP policies on public goods such as information and innovation, some degree of coordination or consensus ideally needs to exist to minimise the likelihood of producing generally negative effects for all or most of the countries involved, including increased inequalities in access and affordability. The most likely scenario for this to occur would be when countries pursue only their short-term national interests. The situation is comparable to that of generalised competitive devaluations in times of crisis: countries apply them in order to increase exports and hence boost production and employment. But if all countries apply the same policy, the result is an overall reduction in international trade and national production.

The results of innovative research into needed medicines should be regarded as a global public good. Under the present system of incentives based on exclusive property rights, public and private investment in R&D is recovered through a temporary monopoly that results in high non-competitive prices. Unless alternative mechanisms are established that delink incentives for innovation from prices, regulators should be aware that pricing can be regarded as a reward for past innovation and incentivizes future R&D. The question remains on how countries with different income levels should contribute proportionately to these incentives. Once this question is resolved or alternative incentives are establish, it would be easier to agree on what an equitable and sustainable international price structure might look like.

A generalised use of ERP where all countries applied the same criterion for determining the national price – be it the minimum or an average price – would lead to price convergence around a single international price of new medicines. But this is not an inevitable effect of ERP. For example, if countries were to apply some form of income-related discount to the average international price, the most likely result would be an international structure of differential, income-related prices. Similarly, if all countries choose a cluster of similar-income countries for ERP purposes, the result would probably be a differential price structure related to the average income of the clusters.

If real prices and pricing mechanisms are not transparent, it is very likely that countries with larger markets and the highest negotiating power end up with the lowest real transaction prices. In that case the international differential price structure might turn out to be regressive, meaning that low-income countries would end up paying lower prices than high-income countries.

6.2 Specific components of an external reference pricing system

The purpose of this section is to provide a check list of the issues and options to be considered when designing an ERP system. An ERP system is built on a set of elements. There is a lot of variety in the way countries can and actually do define these elements. The effects of a particular ERP system will depend on how these components are designed and implemented. Unfortunately, there is not much evidence on the effects of specific ERP systems or components. Moreover, the choice of options will depend on the regulator's particular objectives, the information available, and restrictions that might limit technical capacity. Since it does not seem appropriate to try to define an optimal ERP system, only some pros and cons of possible options for the main issues will be discussed to help potential users build their own system. Table 4 shows the main components of ERP systems, as well as the respective options available for their implementation. The options are often not mutually exclusive, but can be combined. For instance, products priced under the ERP system might include all on-patent products, all reimbursable products or those that are simultaneously on-patent and reimbursable.

Table 4. **Components and issues to consider when designing an External Reference Price System**

Component/issue	Main options
1. Single or multiple approaches to setting the regulated price	- ERP is the only approach - Several approaches are used without specification of how these criteria are related - Several approaches are used and the one providing the lowest price is applied
2. Types of products regulated by ERP	The main options are: - all products - on-patent products - off-patent/generic products - reimbursable products
3. Criteria for deciding the number of countries and for selecting the specific countries used as reference countries	Few vs. many countries Countries with: - low prices - accessible prices - early entry of new medicines - socio-economic similarities - similar policy objectives - neighbouring countries
4. Sources of price information	- Asking applicants for international certificate prices - Public official databases - *Ad hoc* requesting of specific price information to authorities in other countries
5. Type of price used for setting the national target price	- Transaction price vs. list price - Ex-factory price - Importation price - Retail price
6. Formula or procedure to derive the national target price from the prices in reference countries	- Average price (mean) - Average price adjusted by GDP per capita - Median price - Minimum price
7. Exchange Rate	Source, updating
8. Procedure if some country prices are not available when needed	- Use available country prices - Include additional countries not in the list - Use available prices provisionally and revise prices when they become available
9. Updating / revisions of the price based on the ERP procedure	- ERP is used only for setting the initial launch price (other price regulations /interventions may apply later) - The price is periodically updated/revised by the ERP procedure. - If it is to be revised in the future, the criteria and periodicity for updating
10. Enforcement	- Rigid enforcement of computed national price (take it or leave it approach) - Computed national price used as a benchmark for negotiation
11. Monitoring and evaluation	- No monitoring and evaluation - Monitoring and evaluation with variable levels of comprehensiveness and rigour

6.3 Advantages and disadvantages of external reference pricing components

1.   Single or multiple approaches to setting the regulated price

One advantage of using more than one price control mechanism is that if one of them fails in a given case, others are still available. From the point of view of predictability and transparency, it would be preferable to use one single criterion - ERP or any other approach – for regulating the price of a certain type of medicine. This is due to the risk of lack of objectivity, especially if the relationship among the multiple mechanisms applied is not clearly specified. This can be overcome by stating, for instance, the priority of the various mechanisms applied, as long as the information required is available. Alternatively it can be determined that the selected price will be the lowest one of those obtained with the various pricing mechanisms or criteria applied.

2.   Types of products regulated by ERP

In principle, ERP – in fact, any type of price regulation – is probably more justified in the case of on-patent products, as they are by definition less likely to experience competition so driving the price to an efficient level. In practice, competition might also be missing in the markets of multi-source (off-patent) medicines. In fact, most countries do not trust generic competition to automatically reduce prices after market exclusivity of the originator expires, but force prices down by regulation. However, in the case of off-patent medicines there are other price control mechanisms, such as internal reference pricing or linking the price of generics to the originators' price, which might be more appropriate to ERP in terms of the level of the technical capacities and information required to apply them.

ERP – in fact, any type of price regulation – is more frequently used for publicly reimbursed medicines; this is justified by the goal of making an efficient use of public resources. However, it can also be justified in the case of privately funded and out-of-pocket paid medicines – which amount to the majority of medicines consumed in developing countries – as a mechanism to protect consumers from the lack of competition and of potential abuses from monopolists.

3.   Criteria for deciding the number of countries and for selecting the specific countries used as reference countries

A larger number of reference countries will probably provide a more representative sample of prices and minimise the possibility of obtaining a price well above or below the average. Depending on the precise procedure applied, countries that use a small number of countries as reference might be more likely to end up with relatively high prices.

One of the case study countries uses four reference countries (Greece, Spain, Turkey and the country of origin) and it sets its price on the basis of the prices available in those countries at that time. When a new medicine originating in the UK or Germany is available, the company may not want to introduce it in Greece, Spain or Turkey, because these countries have low prices and high transparency. As a result, the price that will be used as the reference will be the one from the country of origin (which normally grants a high price). Using a small number of countries carries, in principle, a higher risk of having only a fraction of the selected countries' prices available at the time the prices have to be set, because the product is not yet in the market of the reference countries. However, a

country unable to apply complex pricing mechanisms might want to link their prices to a few countries that are usually among the first to market new products and that are perceived as doing a good job in regulating prices, for instance, by means of pharmacoeconomic pricing methods for single-source medicines.

The criteria for selecting the reference countries should be consistent with the objectives of price regulation. Price availability is a pragmatic criterion, but it can lead to biased results if a company's strategy to distort price information through confidential discounts and other approaches succeeds and if companies launch new products in high-price countries first. Choosing countries of the same region and of similar socio-economic characteristics is a practical criterion which is likely to legitimise the method and the prices obtained. However, a low-income country might choose to take a set of higher-income countries that apply other, well-founded pricing methods as a reference and then adjust the resulting price according to a price differential based on the income differential.

4.   Sources of price information

A good practice for ensuring the availability of valid, reliable price information is to combine the use of national and international data sources with the requirement that applicant companies provide certified information on the prices they charge for the product in the reference countries and set substantial penalties for companies that provide erroneous information.

There are many public databases, but the prices available are normally official list prices and not real transaction prices. Informal communications with national price and reimbursement authorities is a valuable complementary source of pricing information.

5.   Type of price used for setting the national target price

One of the most important issues to be dealt with when designing and applying ERP is related to the nature and relevance of the price information, i.e. on the use of list/catalogue prices vs. actual transaction prices. List, catalogue or nominal price usually refers to a theoretical or virtual price, which might be recorded in documents but does not reflect the actual terms of the exchange of the transactions. Transaction, actual or real price refers to the actual exchange relationship and reflects the economic concept of opportunity cost. Where discounts (per product unit) are applied, it is easy to calculate the transaction price if the list price and the discount are known: a list price of €50 to which a 4% discount is applied, would have a real/transaction price of €48. But the calculation becomes more complicated and sometimes arbitrary in the case of annual rebates, as the price per unit must refer to an average over a certain period and can only be computed ex-post. In the case of pay-back mechanisms, the issue is more complex, as it might not be possible to allocate the pay-back to each single product. The situation is still more complicated when the buyer obtains other concessions as incentives: for instance, no discount for the product concerned, but other medicines or goods either discounted or free, such as equipment etc. All these practices tend to reduce price transparency and bias observed prices.

The role of margins and mark-ups is another issue to be considered in the application of ERP. In theory, ERP can be applied to a price from any stage in the distribution chain: importer, manufacturer (ex-factory), wholesale, retail (consumer), with or without taxes. But if the main rationale of ERP is to avoid suppliers charging a given country unjustifiably higher prices than in other countries, the logical focus of ERP should be importer or ex-factory prices. International retail price differences caused by differences in mark-ups and taxes cannot be attributed to the manufacturer, but to national

distributors and to national policies, or to the absence of the latter. Therefore, ERP usually focuses on ex-factory or import prices. However, the prices that appear on the available information sources (e.g. national websites) are sometimes retail prices. This is not a big problem as long as mark-ups in the reference countries concerned are regulated and actually enforced, because in that case they will probably be known and hence the calculations are relatively simple. Otherwise, the adjustment will have to be made on the basis of average mark-ups estimated through sampling studies.

A different but interesting question is whether it would make sense for a country with unregulated mark-ups to regulate the retail or consumer price with ERP or any other method. This would mean that the percentage of the retail price by each intermediary in the distribution chain would be the result of negotiation and relative market forces. The approach would probably be acceptable in a competitive environment, but it would be more questionable if one of the parties had disproportional market power and could impose an unfair distribution of the price.

6.   Formula or procedure to derive the national target price from the prices in reference countries

The effects of ERP will be very different depending on whether the price selected is the median, a simple or weighted average, or the lowest price found among the reference countries. It can be tempting to assume that the lowest price found in any country can legitimately apply elsewhere. But this is a simplistic approach: a very low price might reflect the special treatment of a low-income country by a company based on humanitarian or social corporate responsibility considerations. It can also be justified by large sales and/or orders, or it can be the result of decisions that do not depend on the company, such as price cuts or variations in exchange rates.

If the prices in reference countries relate to medicine available in other strengths, pack sizes, etc., some procedure should be set up to convert those prices into a convenient unit price, for instance, price per tablet / capsule or price per mg. or ml. of active ingredient, that can be applied to the presentation to be priced.

7.   Exchange rate

As reference prices will usually be expressed in difference currencies, exchange rates will be required to convert the reference country prices into the national currency. It seems advisable to use the current exchange rates from an official source, e.g. the central bank.

8.   Procedure to follow if international prices are not available at the time they are needed

When prices in some reference countries are not available at the time the price is to be set, the best practice is probably to grant a provisional price in order not to delay the entry of a valuable new medicine, and to revise the provisional price when the missing prices become available. This approach would also partly counteract the possible use of strategies by pharmaceutical companies to delay the launch of new products in low-price referenced countries.

9.   Updating / revisions of the target national price based on ERP

It could be argued that if using ERP, the regulated price should be regularly updated if the prices in the reference countries or the exchange rates change. This would, however, require a lot more work, unless a quasi-automatic information system could be set up. A compromise could be to only update the prices of new and/or high cost medicines, for example.

10.   Enforcement

In general it seems advisable that the link between price calculation and price setting be a direct and clear one. However, there is a risk that a strict enforcement of the calculated price may lead companies to decide not to market valuable medicines in a country - an undesirable outcome from the point of view of public health, often unsustainable from a political perspective. In that case it would be advisable to specify the extraordinary reasons why the calculated price was not strictly applied.

11.   Monitoring and evaluation

As has been repeatedly mentioned in this document, ERP might not always attain its intended effects and is likely to have some undesirable effects. It is advisable therefore that countries applying ERP introduce ways to monitor and evaluate the effect of the policy. At the very least, monitoring the effects of ERP implies a need to collect price information before and after its implementation. The evaluation would require the availability of price information for a set of countries, some applying and some not applying ERP. The design of such an evaluation cannot be a simple before and after comparison of prices, as other factors and policies might be affecting prices and should be controlled for. Ideally a rigorous evaluation should be done as a joint exercise by a large number of countries coordinated by an independent organization.

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Review Series on Pharmaceutical Pricing Policies and Interventions. Working Paper 1: External Reference Pricing

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References

1. *Pharmaceutical Pricing Policies in a Global Market*. OECD Health Policy Studies, OECD, 2008. [Access 20 June 2009]. Available at: http://www.oecd.org/document/36/0,3343,en_2649_33929_41000996_1_1_1_37407,00.html

2. Espin J, Rovira J. Analysis of differences and commonalities in pricing and reimbursement systems in Europe. 2007. [Access 21 June 2009]. Available at: http://www.easp.es/web/Documentos/OtrosDocumentos/EASPReportPandREurope.pdf

3. PPRI Glossary: Internal price referencing. Available from: http://ppri.oebig.at/index.aspx?Navigation=r|4-v

4. Garcia-Mariñoso B, Jelovac I, Olivella P. External referencing and pharmaceutical price negotiation. In: Économique GGdedT, 2008. Available at SSRN: http://ssrn.com/abstract=1168822

5. Simoens S. International comparison of generic medicine prices. *Current Medical Research and Opinion*, 2007, 23:2647-54.

6. Danzon PM, Furukawa MF. Prices and Availability of Biopharmaceuticals: An International Comparison. *Health Affairs*, 2006, 25:1353-1362.

7. Danzon PM, Furukawa MF. Prices and availability of pharmaceuticals: evidence from nine countries. *Health Affairs*, 2003 (Web Exclusives):W3-36.

8. Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs - evidence from twenty-five major markets in the 1990s. *Health Economics*, 2005, 14:269-92.

9. Dukes MNG, Haaijer-Ruskamp F, Joncheere CP, Rietveld AH. *Drugs and Money*. Geneva, World Health Organization, 2003.

10. International pharmaceutical price differences. Australian Productivity Commission study. Melbourne, Canberra, 2001.

11. Pharmaceuticals: Cost containment, Pricing, Reimbursement. HNP brief, World Bank, 2005. Available from: http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1109774792596/HNPBrief_7.pdf

12. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. *International Journal of Health Care Finance and Economics* 2003, 3:183-205.

13. Garattini L, Cornago D, De Compadri P. Pricing and reimbursement of in-patent drugs in seven European countries: a comparative analysis. *Health Policy*, 2007, 82:330-9.

14. *Drug Evaluation and Pricing*, a presentation by Y. Inazumi, Chief of Drug Price, Economic Affairs Division, Health Policy Bureau, Ministry of Health, Labour and Welfare, Japan, in Paris, March 2008.

15. Moïse P, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Mexico. [Access 21 June 2009]. Available at: http://www.oecd.org/dataoecd/39/36/38097348.pdf

16. Kaló Z, Docteur E, Moïse P. Pharmaceutical pricing and reimbursement policies in Slovakia. [Access 6 June 2010].
Available at: http://www.republiqueslovaque.com/secteur/pharma-pricing-slovakia-ocde.pdf

17. Kanavos P, Vandros S, Habicht J, de Joncheere K. Review of the Estonian Pharmaceutical Sector: Towards the development of a National Medicines Policy. [Access 7 june 2010]. Available at: http://www.euro.who.int/en/where-we-work/member-states/estonia/publications3/review-of-the-estonian-pharmaceutical-sector-towards-the-development-of-a-national-medicines-policy

18. Kyle MK, Allsbrook JS, Schulman KA. Does Reimportation Reduce Price Differences for Prescription Drugs? Lessons from the European Union. Health Services Research, 2008, 43:1308-24.

19. Danzon PM, Epstein AJ. Effects of Regulation on Drug Launch and Pricing in Interdependent Markets. National Bureau of Economic Research, Inc, NBER Working Papers: 14041, 2008.

20. Jack W, Lanjouw JO. Financing Pharmaceutical Innovation: How Much Should Poor Countries Contribute? World Bank Economic Review, 2005, 19:45-67.

21. Richter A. Assessing the impact of global price interdependencies. *Pharmacoeconomics*, 2008, 26:649-59.

22. Stargardt T, Schreyogg J. Impact of cross-reference pricing on pharmaceutical prices: manufacturers' pricing strategies and price regulation. *Applied Health Economics and Health Policy*, 2006, 5:235-47.

23. European Commission. Pharmaceutical Sector Inquiry. 2008.

Background material

Aaserud M, Austvoll-Dahlgren A, Kösters JP, Oxman AD, Ramsay C, Sturm H. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database of Systematic Reviews, 2006.

Administration UDoCIT. Pharmaceutical Control in OECD Countries. Implications for US Consumers, Pricing, Research and Development, and Innovation. Department of Commerce. USA, 2004.

Andersson F, Hertzman P. Effective Patent Life of Drugs in Sweden - A Comparison with International Studies. *Managerial and Decision Economics*, 1993, 14(1):53-63.

Andersson F. The International Diffusion of New Drugs: A Comparative Study of Seven Industrialized Countries. *Journal of Research in Pharmaceutical Economics*, 1992, 4(2):43-62.

Anis AH, Wen Q. Price Regulation of Pharmaceuticals in Canada. *Journal of Health Economics*, 1998, 17(1):21-38.

Babar ZUD, Ibrahim MI, Singh H, Bukahri NI, Creese A. Evaluating drug prices, availability, affordability, and price components: implications for access to drugs in Malaysia. PLoS Med, 2007, 4(3):e82.

Babar ZUD, Ibrahim MIM, Bukhari NI. A Pricing Analysis of Cardiovascular and Blood Products after Privatization of Drug Distribution System in Malaysia. *Journal of Pharmaceutical Finance, Economics and Policy*, 2005, 14(3):3-25.

Bardey D, Bommier A, Jullien B. Retail price regulation and innovation: reference pricing in the pharmaceutical industry. *Journal of Health Economics*, 2010, 29:303-316.

Barros PP, Martinez-Giralt X. On International Cost-Sharing of Pharmaceutical R&D. *International Journal of Health Care Finance and Economics*, 2008, 8:301-12.

Bloom N, Reenen JV. Regulating drug prices: Where do we go from here? *Fiscal Studie*s, 1998, 19:321-342.

Brekke KR, Helge Holmas T, Rune Straume OD. Are Pharmaceuticals Still Inexpensive in Norway? A Comparison of Prescription Drug Prices in Ten European Countries. The Institute for Research in Economics and Business Administration (SNF Samfunns- og næringslivsforskning). Bergen, May 2010.

Capri S, Levaggi R. International Price Regulations in the Pharmaceutical Sector: A Common Model to Sharing Cost and Benefits. *Journal of Pharmaceutical Finance, Economics and Policy*, 2006, 15:21-40.

Cheap drugs? WHO intervenes. *Annals of Oncology*, 2001, 12(4):426-7.

Chintagunta PK, Desiraju R. Strategic Pricing and detailing behavior in international markets. *Marketing Science*, 2005:67-80.

Cohen J, Faden L, Predaris S, Young B. Patient Access to Pharmaceuticals: An International Comparison. *European Journal of Health Economics*. 2007, 8:253-66.

IMS Consulting. A Comparison of Pharmaceutical Pricing in Switzerland with selected reference countries. 2003.

Danzon PM, Furukawa MF. International prices and availability of pharmaceuticals in 2005. *Health Affairs*, 2008, 27:221-233.

Gray A, Matsebula T. Drug pricing in South Africa. [Access 7 June 2010]. Available at. http://www.healthlink.org.za/uploads/files/chapter9_00.pdf

Kotwani A, Ewen M, Dey D, Iyer S, Lakshmi PK, Patel A, et al. Prices & availability of common medicines at six sites in India using a standard methodology. *Indian Journal of Medical Research*, 2007, 125(5):645-54.

Kremer M. Pharmaceuticals and the developing world. *The Journal of Economic Perspectives*, 2002, 16(4):67-90.

Merkur S, Mossialos. E. A pricing policy toward the sourcing of cheaper drugs in Cyprus. *Health Policy*, 2007, 368-375.

Nunn AS, Fonseca EM, Bastos FI, Gruskin S, Salomon JA. Evolution of antiretroviral drug costs in Brazil in the context of free and universal access to AIDS treatment. PLoSMed, 2007, 4:e305.

Paris V, Docteur E. Pharmaceutical Pricing and Reimbursement Polices in Switzerland. OECD Health Working Papers, 2007.

Puig-Junoy J. Incentives and pharmaceutical reimbursement reforms in Spain.
Health Policy, 2004, 67:149-65.

Reich MR, Tavis LA, Williams OF. *Pharmaceutical Corporate Presence in Developing Countries,*
Multinational Managers and Developing Country Concerns, vol. 4. Notre Dame, University of Notre
Dame Press, 1993:83-107.

Reidenberg MM, Walley T. The pros and cons of essential medicines for rich countries.
BMJ, 2004, 329:1172.

Sood N, de Vries H, Lakdawalla DN, Goldman DP. The Effect of Regulation on Pharmaceutical
Revenues: Experience in nineteen countries. *Health Affairs*, 2009, w125-w137.

Spurgeon D. US pharmacists cleared to buy in cheap drugs from Canada. *BMJ*, 2002, 325:183.

Turone F. Italy cracks down on its drugs bill. *BMJ*, 2002, 325:1058.

Ugatch MP. *The International Political Economy of Intellectual Property Rights*. New Horizons in
Intellectual Property Series. Cheltenham, U.K. and Northampton, Mass., Edward Elgar Publishing, 2004.

van Mosseveld C. Pharmaceutical expenditure compared across countries.
Canadian Journal of Clinical Pharmacology, 2005, 12:e269-e75.

Vernon JA. Examining the link between price regulation and pharmaceutical R&D investment.
Health Economics, 2005, 14:1-16.

Willert PL. Assessment of the pharmaceutical market in Poland after accession to the European Union.
European Journal of Health Economics, 2007, 8:347-57.

Yfantopoulos J. Pharmaceutical pricing and reimbursement reforms in Greece.
European Journal of Health Economics, 2008, 9:87-97.

Zajac S, Balaz V. Dual Economy and Impacts of Foreign Investment on Private R&D in Slovakia.
Ekonomicky Casopis/Journal of Economics, 2007, 55:851-72.

Zarocostas J. Countries should encourage use of generic substitutes, says OECD. *BMJ*, 2008, 337:a1996.