The Implementation of External Reference Pricing within and across Country Borders

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List of Acronyms

AUT	Austria
BEL	Belgium
BGR	Bulgaria
BMI	Business Monitoring International
CHE	Switzerland
CRD	Centre for Reviews and Dissemination
CYP	Cyprus
CZE	Czech Republic
DEU	Germany
DNK	Denmark
EFPIA	European Federation of Pharmaceutical Industries and Associations
ERP	External Reference Pricing
ESP	Spain
EST	Estonia
EU	European Union
FIN	Finland
FRA	France
GRC	Greece
HiT	Health in Transition
HRV	Croatia
HTA	Health Technology Assessment
HUN	Hungary
IRL	Ireland
ISL	Iceland
ISR	Israel
ITA	Italy
LTU	Lithuania
LUX	Luxemburg
LVA	Latvia
MDA	Moldova
MLT	Malta
NLD	The Netherlands
NOR	Norway
OECD	Organisation for Economic Cooperation and Development
POL	Poland
PPP	Purchasing Power Parity
PRT	Portugal
R&D	Research and Development
ROU	Romania
RUS	Russia
SRB	Serbia
SVK	Slovakia
SVN	Slovenia
SWE	Sweden
TUR	Turkey
VBP	Value Based Pricing
VED	Vital & Essential Drugs
WHO	World Health Organization
WHO-CC	World Health Organisation Collaborating Centres
WoS	Web of Science

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ABSTRACT

BACKGROUND

External reference pricing (ERP), a frequently implemented pricing policy, seeks to rationalize prices and contain costs by using foreign prices as reference for the determination of domestic prices and facilitation of negotiation. Its use across countries varies significantly in terms of objectives, methods, administration and implementation.

METHOD

A systematic literature review was conducted according to CRD guidelines. 17 Study endpoints were used to identify characteristics of ERP implementation across 29 countries, of which 17 were EU member states. Multiple databases were examined to provide a wide range of ERP sources. After filtering for mention of ERP implementation related to at least one of the 17 study endpoints 176 studies remained. Primary data collection, in the form of questionnaires directed at key stakeholders, were also used to supplement data in instances where information received from the systematic literature review was outdated or minimal. Findings from the systematic literature review and primary evidence from key stakeholders were benchmarked against 14 best practice principles inherent to an optimal ERP system to determine the quality of ERP systems implemented by the countries of interest.

RESULTS

The systematic literature review confirmed that there is heterogeneity in the way that ERP is implemented across countries. There tends to be variation in the size of the country baskets, with larger baskets becoming more common and in the way that countries chose their basket countries – some choose those with similar socioeconomic characteristics whilst others do not. Furthermore there is variation in the calculation used with most countries vying away from the average-based calculations towards the lowest basket price or the average of the lowest 'n' prices. The frequency of price revisions differs according to authorities and government negotiations, as does the rate at which exchange rate fluctuations are taken into account in pricing decisions. In terms of the 14 best practice principles Belgium, France, and South Africa adhered to the most principles whilst Bulgaria, Hungary and Romania had the most instances of non-adherence.

CONCLUSION

Heterogeneity and recent trends in ERP design have policy implications for governments, which include globally declining pharmaceutical prices and other, potentially more undesirable consequences such as launch delays in low-income countries, parallel trade reducing drug stock levels, inflated prices in low-income countries, reduced incentive for continued R&D and reduced access to medicines in some regions. Overcoming this issue to ensure that ERP is beneficial to all stakeholders will require a focus on developing sustainable, transparent, simple and stable systems using a set of key guidelines that should maximise the benefits of the pricing policy.

EXECUTIVE SUMMARY

This paper aimed to highlight differences in the way that 29 countries implement ERP, which aims to contain medicine costs, using a systematic literature review-based process combined with primary evidence from key stakeholders. Of the 29 countries analyzed 17 were European Member States, with the remainder representative of Latin America, South East Asia, the Middle East and North Africa. Secondary data was collected from literature published between 2000 and 2015 on a set of 17 criteria (endpoints) based on the ERP system design. Databases examined included Web of Science (WoS), CINAHL, EconLit, Medline, ProQuest, Cochrane Library and Scopus. Special keywords and a defined search strategy were used to arrive at an initial list of studies. After filtering for mention of ERP implementation related to at least one of the 17 study endpoints 176 studies remained. Primary evidence was collected via questionnaires distributed among key stakeholders. Results of the systematic literature review and of the primary evidence collection were contrasted with analysis of the goals and observed impacts of the different ERP systems to identify optimal design features of ERP systems.

Findings confirmed high levels of heterogeneity between the ERP systems of different countries. Variation was present in many of the 17 endpoints analyzed. For example, some countries use ERP for all medicines, regardless of their patent status, whilst others use it only for in-patent medicines. ERP processes range from formal to informal and from the main to the supportive pricing policy in place in a country. In cases where the process is informal there is limited definition of policy objective and scope which can affect transparency. Country baskets range in size from three to 36 (not including those countries that use prices in the medicine country of origin) whilst very few countries use any kind of wealth adjustment, even if countries are not selected based on financial characteristics. Reference calculations tend to be based on a lowest price in the basket style calculation, rather than an average based calculation. Some countries use ex-factory prices, which do not reflect confidential discounts or rebates, to form the basis of their calculations meaning referenced prices do not reflect reality.

Rapidly evolving healthcare costs and increases in life expectancy and chronic disease prevalence mean that reduced drug prices are the ultimate aim for most country governments. However, badly designed ERP systems can be detrimental to all stakeholders and should be avoided at all costs. ERP systems should be designed with both health and industrial policy aims in mind to ensure that the requirements of all stakeholders including patients, manufacturers and governments are represented in order to ensure that patients get access to well-priced medicines as and when required, governments can spend within their means and manufacturers have enough incentive to continue investing in future R&D in order to benefit future patient populations.

There are a number of key criteria that can be adhered to that may ensure an ERP system is designed to benefit all stakeholders and remains transparent, simple, stable and sustainable. These criteria are based on the selection of reference countries and prices; the use of exchange rates; the types of products for which ERP should be used; price revisions; and the derivation of target prices. Furthermore, as no two countries are identical any EPR system should outline the objective and scope of the ERP system and ensure it reflects the overall healthcare system's values and objectives. It is also recommended that target prices should align with the expected value of the product, determined by using HTA or a similar mechanism. Encouraging countries to follow such guidelines could ensure that ERP systems do not alienate the innovative pharmaceutical company and ensure that they are incentivized to continue investing in global R&D which in the long run will maximize global population health. In this paper, 14 basic principles that an optimal ERP system should follow were benchmarked against the findings from the systematic literature review and primary evidence from key stakeholders to determine the quality of ERP systems implemented by the countries of interest. Belgium, France, and South Africa adhered to the most principles whilst Bulgaria, Hungary and Romania had the most instances of non-adherence.

1. INTRODUCTION

ERP, also known as external price referencing or international price comparison/ benchmarking, is a widely used pricing policy with high global research interest. It is introduced when governments decide to use foreign drug prices to regulate domestic prices (EFPIA, 2014; Danzon and Towse, 2003) and to impose price caps based on prices of similar drugs in other reference countries (Houy and Jelovac, 2014) with the official definition being: "the practice of using drug prices in several countries to derive a benchmark or reference price for the purposes of setting or negotiating prices in countries" (WHO, 2013; EFPIA, 2014). The primary aim of the pricing mechanism is to control in-patent drug prices (Ruggeri and Nolte, 2013) via the containment of pharmaceutical prices and expenditure (Espin et al., 2010). The widespread use of ERP generally arises due to government cost control requirements. Authorities can use international comparisons to evaluate the fairness or appropriateness of the actual price related to comparative cases (OECD, 2008). Specifically, drug prices in other countries are used as a reference to determine a limit for the entry price of a drug or reimbursement price (Nguyen et al., 2015).

The implementation of ERP varies significantly between countries in terms of the various rules followed by individual countries to calculate the final product price (Espin et al., 2014). For example, an increase in the number of reference countries in a basket generally leads to further reductions in drug prices (BMI Research, 2010). Furthermore, the countries used in the basket can affect price variation. Financial performance of the country, pharmaceutical pricing systems, publication of actual versus negotiated or concealed prices, exact comparator products and disease burden of the potential reference country all need to be taken into account when choosing reference countries (WHO, 2015).

Although ERP may have the potential to contribute to improved access and counteract affordability problems sometimes seen in lower-income countries, there are potential consequences. The most significant concern is related to the fact that ERP could lead high-income countries to demand low prices creating resulting difficulties for low-income countries. ERP-related price leakages can trigger a manufacturer to set either a single price or narrow band of prices before launch is allowed. Such linking of low and high income markets can lead to prices converging at a higher level than would have been the case if markets had been separate. In low-income countries, this can lead to inappropriately high prices and reduced access for patients. In high-income countries, whilst in the short run imported lower prices may be beneficial, in the long run, lower revenues can lead to reduced return on R&D investment and consequently fewer new medicines (Danzon and Towse, 2003). Furthermore, marketing authorization holders may prefer initially to promote their products to high-price countries rather than low-price countries so that these high prices are used as references in countries performing ERP (Vogler et al., 2015). At the same time, the accuracy of international comparisons may be distorted due to methodological issues and differences across countries in strength, formulation and pack sizes available (Timur and Picone, 2010). ERP assessment is considered complex compared to other pricing methods. The promotion of transparency around the use of ERP may improve the accountability of decision-making, which could reduce uncertainty for manufacturers and eliminate discrimination and corruption (Espin et al., 2014).

There is a need to study the implementation of ERP with a focus on differences in implementation across countries. The present study will attempt, via a combination of primary and secondary evidence, to contribute to the review, analysis and body of information about ERP structure and its alignment with other policies across countries where the following countries are of interest: Austria, Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Turkey, Brazil, Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, South Africa, South Korea and United Arab Emirates. To determine the quality of ERP systems implemented by the countries of interest we benchmark findings from the systematic literature review and primary evidence from key stakeholders against 14 basic principles that an optimal ERP system should follow (Sullivan et al., 2017).

2. METHODS

Both primary and secondary evidence have been used to identify characteristics of ERP implementation across 29 countries and to inform the discussion and analysis in the sections that follow. Secondary evidence was collected via a systematic literature review, which was carried out based on the CRD guidelines for systematic reviews.

2.1 STUDY ENDPOINTS

A number of defined endpoints relating to the structural elements of ERP were analysed in this systematic literature review (see Table 1). The main role of ERP in each country of interest was analysed in order to determine differences in application across countries. Transparency was evaluated to examine fairness in pricing. We also investigated the role of stakeholders in the design of ERP systems and their involvement in any appeals processes. The number of basket countries and the criteria used for their selection was also analysed alongside the methods used for price calculation. The role of the patent status and innovation was taken into account. Furthermore, investigation around the inclusion of wealth adjustments, price revisions and exchange rate fluctuations was necessary given their impact on price determination (Toumi et al., 2014). The sources, dissemination and accessibility of price data were also assessed as key issues in price setting. As far as interaction with other policies is concerned, the alignment of the pricing process with the reimbursement process was examined and the combination of ERP with different negotiation tools for reimbursement was used as an endpoint. The interaction of other pricing processes such as value based pricing (VBP) and health technology assessment (HTA) with ERP was also examined.

Table 1: Definition of endpoints in ERP implementation

Endpoints	Definition
Structural Elements	
Objective and alignment with health system objectives	Assesses the aim of international comparisons and the relationship with health systems' objectives
Characteristics of pharmaceuticals subject to ERP	Takes into account the categories of drugs included in the ERP system
Main role	Determine whether ERP provides the major or supportive role in negotiations and determination of drug prices
Transparency	Includes the legislative criteria used by countries to promote a fair pricing process
Competent authorities in ERP implementation	Presents the authorities in control of ERP policy implementation
Appeals by stakeholders to regulator decisions	Assesses the possible appeals of stakeholders in pricing process
Number of basket countries and countries in the basket	Presents the countries and the number of members included in each basket
Criteria for basket country selection	Assesses the appropriate criteria to select reference countries
Type of comparator price	Presents the selection of price category across countries
Method for calculation of the reference price	Examines the different methods of countries to determine reference price
Sources of information for pricing decisions	Presents the sources and stakeholders that contribute to public access of price data
Inclusion of wealth adjustments	Assesses whether wealth adjustments made to the reference price when countries of higher or lower GDP are included in the basket
Accounting for exchange rate fluctuations	Assesses whether calculations used to account for exchange rate fluctuations across countries
Interaction with other policies	
Link between price and reimbursement	Refers to the countries that take into account price determination and reimbursement process at the same time
Interaction with HTA or VBP	Assesses the parallel use of international comparisons with other methods to set drug prices
Alignment with other negotiation tools of reimbursement	Refers to the combination of international comparisons with reimbursement purposes
Link between ERP regulation and patent status	Takes into consideration the role of patent status in ERP price calculation

2.2 SYSTEMATIC LITERATURE REVIEW: DATA SOURCES, SEARCH STRATEGY AND KEYWORDS

Both peer-reviewed and grey literature were examined to minimize bias and identify all relevant information. Multiple databases were utilised, these were the Web of Science (WoS), CINAHL, EconLit, Medline, ProQuest, Cochrane Library and Scopus. A combination of broad and policy key words were used to ensure that all relevant literature was captured. All synonyms and different phrasings of ERP or External Price Referencing were included in the search. The search run was ("Pharmaceutical Price Regulation" OR "Pharmaceutical Regulation" OR "Cost Containment" OR "Pharmaceutical Pricing" OR "External Price Referencing" OR "External Price Referencing" OR "International Price Comparisons" OR "International Reference Pricing" OR "International Price Referencing") AND (drug OR drugs OR medicine OR medicines OR pharmaceutical OR pharmaceuticals). The search was restricted to keywords present within abstracts only, to limit the number of irrelevant papers being returned. When searching the WoS, the search terms were restricted to title only, as the option to restrict to abstract was not available. This study includes only papers in English. There were no restrictions in terms of country in the initial search to ensure that evidence is representative of a wide geographical range. However, once the search was concluded, the study was limited to the following countries: Austria, Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Turkey, Brazil, Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, South Africa, South Korea and United Arab Emirates. Our study included literature published from 2000 to 2016.

We also completed a targeted and comprehensive search of the WHO, the WHO collaborating Centre for Pharmaceutical Pricing and Reimbursement policies and the OECD online databases to ensure that no valuable reports were excluded. The key words used to search these were "External Price Referencing" OR "External Price Referencing" OR "International Reference Pricing" OR "International Price Referencing". Relevant information was recorded and combined with the results of the systematic literature review. Finally, additional literature gathered from contacts was also included.

2.3 STUDY SELECTION, DATA EXTRACTION, EVALUATION AND SYNTHESIS

The results were filtered according to title and abstract relevance to the topic. Papers with relevant titles were downloaded for further examination. In order to arrive at a final set of studies, the main body of these texts was assessed according to the following criterion: mention of ERP implementation relating to at least one of the selected endpoints. The number of studies based on evidence at each endpoint was noted with cases where some papers related to multiple endpoints, and were therefore referenced multiple times, being taken into account.

An excel spreadsheet was used to extract the relevant information on each endpoint for the selected studies. It includes paper titles in the rows, endpoints in the columns and significant information from the texts being extracted and entered into the respective cells. A comprehensive synthesis of the literature was carried out to identify key trends related to ERP implementation across countries. Results from other systematic literature reviews were included if the selected endpoints in the review were different to the respective endpoints in this study. This process is significant in order to minimize bias of results.

2.4 PRIMARY DATA COLLECTION

As evidence drawn from the systematic literature review was not conclusive, primary evidence was collected to complement the secondary evidence findings. Primary evidence was gathered via questionnaires distributed to key stakeholders in all study countries, from which there were returns from 21 countries i.e.: Belgium, Bulgaria, Jordan, Qatar, Italy, Brazil, South Africa, Romania, Slovenia, Spain, Germany, Egypt, Latvia, Poland, Portugal, Russia, Hungary, Greece, France, Estonia and Slovakia. Respondents included representatives from government agencies, industry representatives and academics, all of whom expressed personal views on how ERP is implemented in their respective countries. Beyond understanding the characteristics of ERP in different settings, other important endpoints, such as the national and international effects of implementing ERP, were addressed in the questionnaires to increase understanding of how

different ERP systems perform against 14 basic principles that each country should follow to achieve an optimal ERP system (see Appendix 1) (Sullivan et al. 2017). The questionnaire was divided into four sections in order to address specific thematic areas around ERP and its use within specific jurisdictions. These areas were (i) Objectives and Scope of External Price Referencing Systems, (ii) Administration and Operations, (iii) Methods for the Conduct of External Price Referencing, and (iv) Implementation of External Price Referencing.

A combination of both primary and secondary evidence is presented in the results section. When evidence from the systematic literature review was used, primary data were used to validate the findings. In cases where minimal or outdated evidence was drawn from the systematic literature review, primary data was used.

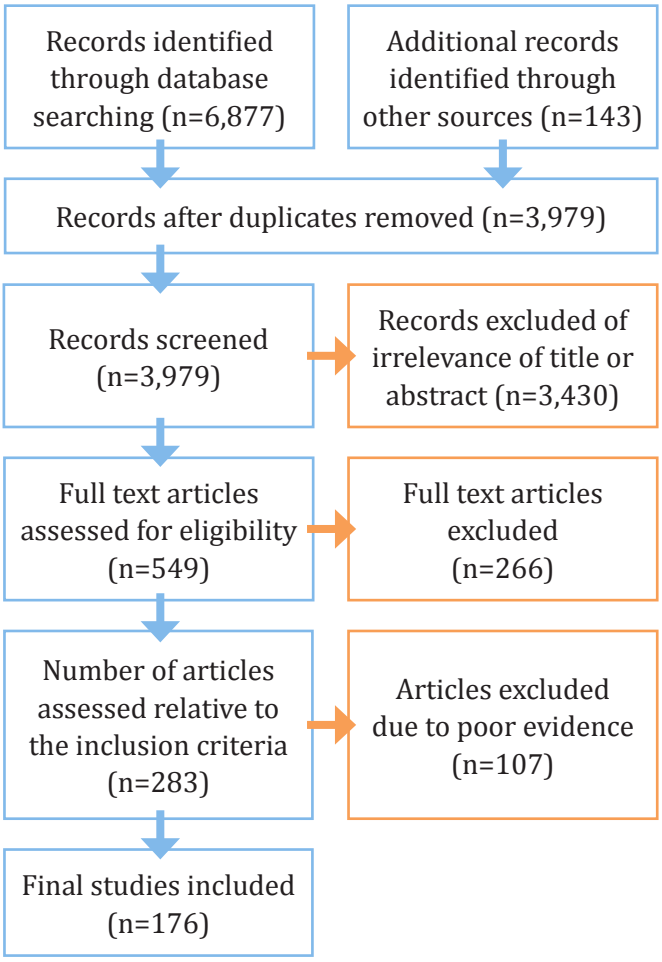
Findings from both primary and secondary evidence were then benchmarked against a framework of 14 basic principles (Sullivan et al. 2017), which countries should follow in order to achieve an optimal ERP system (Appendix 1).

3. RESULTS

3.1 RESULTS OF THE LITERATURE REVIEW

The database search yielded 6,877 studies and the results of the systematic literature search were combined with the results from the search of the WHO, the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement policies and the OECD online databases. Additional literature was provided by our network. 3,979 studies remained and were screened based on relevant titles and abstracts by removing the duplicates using EndNote software (see Figure 1). From the 3,979 studies, 3,526 were peer-reviewed papers and 453 were grey literature. 549 papers were then downloaded and assessed for eligibility. Many studies were excluded because they did not relate to ERP, others because they referred to internal reference pricing or because only the abstract was available, rather than the full text. The main body of 283 texts was then assessed. The detailed analysis of the studies providing evidence on each of the endpoints included can be seen in Table 2. 176 papers were included as final studies in this systematic literature review, a significant proportion of which were grey literature (138 studies) with only 38 peer-reviewed papers (Table 2). Throughout the text, the evidence shown in the tables refers to the latest available source.

Figure 1: PRISMA flow diagram with search results from the systematic literature review



3.2 OBJECTIVE OF ERP AND ALIGNMENT WITH HEALTH SYSTEM OBJECTIVES

ERP is a commonly implemented pricing policy, related to the use of prices of similar drugs to set and benchmark domestic prices (BMI Research, 2012). Generally, ERP has three main aims (Kanavos et al., 2010): (a) negotiate or set prices within a country, (b) negotiate coverage and reimbursement and (c) authorize product marketing. The use of ERP has increased significantly as a price control method (Kanavos and Vandoros, 2011) in in-patent medicines and as a cost containment measure due to issues like the global financial crash in 2008, the increase in life expectancy and the increase in prevalence of chronic conditions (Rémuzat et al., 2015).

The general aim of ERP is the attainment of low domestic prices to limit pharmaceutical spend. For instance, Greece implemented price controls through ERP to limit pharmaceutical and budget spending (Economou, 2010), Turkey introduced ERP in order to control drug expenditure (BMI Research, 2016), Slovenia uses ERP as a tool to regulate the growth of public and private drug expenditure (Albrecht et al., 2009), and in 2010, Russia promoted ERP to regulate prices (Popovich et al., 2012). In Spain, ERP was implemented to control drug prices for which there are no alternatives available on the market (Rémuzat et., 2015); Latvia implements ERP to reimburse drugs at manufacturer prices (Behmane, 2007); and in Bulgaria, ERP aims to estimate a ceiling price for innovative and generic prescription drugs (Kazakov, 2007). In 2004, the Turkish government introduced ERP to contain pharmaceutical expenditure.

However, complicated interrelations between countries can lead to issues around the achievement of these low prices (Barros et al. 2010) due to variations in the basket of reference countries,

Table 2: Results of systematic literature search by source

	CINAHL	Cochrane Library	Econ-Lit	Pro-Quest	Pub-Med	Scopus	WoS	OECD	WHO	WHO-HiT	WHO CC-PPRI	Net-work
No. of original studies	**30**	**11**	**26**	**2,169**	**58**	**684**	**796**	**10**	**18**	**60**	**68**	**49**
Peer-Reviewed studies	30	11	17	1,899	58	678	796	-	-	-	-	37
Grey Literature	-	-	9	270	-	6	-	10	18	60	68	12
No. of studies with relevant titles & abstracts	**6**	**1**	**6**	**299**	**12**	**39**	**40**	**10**	**18**	**32**	**37**	**49**
Peer-Reviewed studies	6	1	6	29	12	39	40	-	-	-	-	37
Grey Literature	-	-	-	270	-	-	-	10	18	32	37	12
No. of studies that match endpoints	**2**	**0**	**1**	**104**	**5**	**15**	**10**	**10**	**18**	**32**	**37**	**49**
Peer-Reviewed studies	2	-	-	11	4	15	10	-	-	-	-	37
Grey Literature	-	-	1	93	1	-	-	10	18	32	37	12
No. of studies that match ERP Impact endpoints	**2**	**0**	**0**	**87**	**2**	**6**	**7**	**8**	**2**	**15**	**27**	**19**
Peer-Reviewed studies	2	-	-	7	2	6	7	-	-	-	-	14
Grey Literature	-	-	1	80	-	-	-	8	2	15	27	5

the type of price compared, calculation methods employed, exchange rate fluctuations and data availability (European Commission, 2015). Another paper in this series examines the impact of variations in ERP system design within- and across-countries on a number of different endpoints including pharmaceutical price levels, launch delays and price convergence (Kanavos *et al.*, 2017)

3.3 CHARACTERISTICS OF PRODUCTS SUBJECT TO ERP PRICE REGULATION

There are a number of variations in terms of the type of medicines subject to ERP systems. For example, the system can focus only on in-patent, originator drugs that are reimbursable (included in the national positive list), or, less commonly, on off-patent, generic drugs that are paid out of pocket. Generally the use of ERP is limited to originator products (Leopold et al. 2012, WHO 2015) but it can be applied to all marketed medicines, or particular categories of medicines such as reimbursable medicines, prescription-only medicines or innovative medicines (European Commission, 2015 and WHO 2015) (Table 3). According to the recommendations of EFPIA (2014), ERP should be limited to in-patent medicines because: (a) More dynamic and effective methods can enhance competitive prices in the off-patent market (b) Price comparison between in-patent and off-patent drugs undermines patent protection and intellectual property characteristics.

Whilst there is some evidence describing the type of medicines covered by ERP policies in individual countries (see Table 3), ERP implementation mainly relates to reimbursable medicines (Vogler et al., 2008); Bulgaria, Romania, Slovenia and Poland set prices for generic prescribed drugs based on international reference pricing policy (Kazakov, 2007). Russia refers to retail prices of publicly

Table 3: Type of pharmaceuticals subject to ERP across countries

	Pharmaceuticals subject to ERP			
	All medicines (regardless of inclusion in the national positive list)	**Only medicines included in the national positive list**	**In-patent drugs only**	**All drugs regardless of patent status**
Austria		✓		✓
Belgium	✓		✓	
Bulgaria		✓		✓
Czech Republic		✓		✓
Estonia		✓	✓	
France		✓	✓	
Germany		✓	✓	
Greece		✓	✓	
Hungary		✓	✓	
Italy		✓	✓	
Latvia		✓		✓
Poland		✓		✓
Portugal		✓		✓
Romania	✓			✓
Slovakia		✓		✓
Slovenia		✓		✓
Spain		✓	✓	
Egypt	✓		✓	
Jordan	✓			✓
Kuwait				
Lebanon				✓
United Arab Emirates	✓			✓
Brazil			✓	
Russia		✓		✓
South Korea			✓	
Turkey	✓		✓	
South Africa			✓	

Sources: The authors, adapted from secondary and primary evidence

reimbursed medicines (Rudisill et al., 2014); Latvia, Poland and Austria use reimbursed drugs (Espin et al., 2014); and Portugal excluded hospital drugs from ERP, and Austria includes outpatient drugs in the ERP system (Rémuzat et al. 2014). Many countries do not specify officially whether ERP is used for the in-patent or off-patent market.

3.4 IS ERP THE MAIN PRICING POLICY OR A SUPPORTIVE TOOL?

Our analysis showed that 29 EU countries implemented ERP as a major or supportive criterion in price determination (European Commission, 2015; Paris and Belloni, 2013; Mossialos et al., 2006), either formally or informally (OECD, 2008), 16 of them use

international comparisons as a core concept, while some countries focus on specific sectors or specific medicines. The countries of interest are presented in Table 4 below.

Russia seeks to inform pricing rules through ERP unofficially (Rudisill et al., 2014). In Belgium ERP is used as a supplementary tool, although comparisons have resulted in price reductions in reimbursed patented drugs over the last five years (Toumi et al., 2014). Germany introduced ERP to control reimbursement prices, while Italy changed the role of ERP from the major to a supplementary method

Table 4: Main Role of ERP

ERP as main (M) or supportive (S) method	
Austria	M
Belgium	S
Bulgaria	S
Czech Republic	M
Estonia	S
France	S
Germany	S
Greece	M
Hungary	S
Italy	S
Latvia	S
Poland	S
Portugal	M
Romania	M
Slovakia	M
Slovenia	M
Spain	S
Egypt	M
Jordan	M
Kuwait	M
Lebanon	M
Qatar	M
Saudi Arabia	M
United Arab Emirates	M
Brazil	S
Russia	S
South Korea	S
Turkey	M
South Africa	M

Sources: The authors, adapted from secondary and primary evidence

to facilitate negotiations between industry and the Medicine Agency (Martini et al., 2012, Ferre et al., 2014). In Poland ERP serves only a complementary role to control the expenditure of the National Health Fund (Janiszewski and Bondaryk, 2007). In Slovenia ERP is the main policy used to determine maximum allowed prices, but it is also used in a supplementary role when prices are set at a particularly high or low level (European Commission, 2015).

3.5 TRANSPARENCY OF ERP PRICING POLICY

An ideal ERP system would be a transparent, administratively simple process requiring minimal information input (Kanavos et al., 2010) based on statutory pricing rules and regulations (Leopold et al., 2012). In reality ERP implementation contains a number of composite points which can be resource intensive and administratively complex, resulting in poor transparency. The level of transparency can be enhanced by specifying the basket of countries and improving the accessibility of pricing data sources used by countries for the referencing process. The estimation of medicine prices based on price caps or on the reference country average promotes predictability for industry, while flexible negotiations between authorities and industry may lead to a less transparent procedure (OECD, 2008). Many low-income countries face difficulties in achieving transparency as they lack a reliable historic and systematic data source on medicine prices (Nguyen et al., 2015). This can lead to ERP system distortion, as decisions will be based on virtual prices. It is difficult to find information on the level of ERP system transparency in different countries but the systematic literature review completed here showed that countries like Austria, Portugal have highly transparent, well-established processes (Toumi et al., 2014) whilst countries like Estonia have reduced transparency (Table 5).

3.6 COMPETENT AUTHORITIES RESPONSIBLE FOR ERP IMPLEMENTATION

ERP systems are implemented by different authorities across different countries. In some countries, ERP lies in the jurisdiction of the Ministry of Health and in others pricing committees or medicines associations are responsible for the process (see Table 6).

Table 5: Transparency in ERP across countries

Transparency in price setting	
Austria	Well-established process
Bulgaria	Lack of transparency
Estonia	Insufficient granularity on the ERP rules
France	See note below[1]
Germany	Insufficient granularity on the ERP rules
Italy	Pricing and reimbursement not straightforward. Conflict between government and industry
Portugal	Introduction of well-established pricing rules[2]
Saudi Arabia	Concern related to the weight of different factors in estimating prices
Russia	Ministry of Health and Social Development of Russia provide official prices for drugs to consumers, which are included on the essential medicines list.

Notes: [1]In France, ERP is a part of an agreement between the Healthcare Products pricing committee and the pharmaceutical companies (Toumi et al., 2014). The use of France as a reference country led authorities and industry to find many incentives in order to induce hidden price payback rules. As a result, authorities can buy medicines at a reasonable price and industry can benefit from participation in a large market. Nevertheless, applied discounts can create a gap between the actual and nominal price, while the actual price is not public in France. [2]Portugal have promoted defined rules about price comparisons in case of non-availability of similar drugs in the reference countries. (Leopold et al., 2012).

Sources: The authors, adapted from secondary and primary evidence

Table 6: Competent authorities in ERP implementation across countries

Authorities	
Austria	The Pricing Committee of the Federal Ministry of Health and Women's Issues
Belgium	Ministry of Economic Affairs
Bulgaria	National Council for Pricing and Reimbursement of Medicinal Products (NCPR)
Czech Republic	State Institute for Drug Control (SUKL)
Estonia	Ministry of Health
France	Comité Economique des Produits de Sante (CEPS)
Germany	National Association of Statutory Health Insurance Funds
Greece	EOF and Pricing committee of MOH
Hungary	National Health Insurance Fund Administration (OEP)
Italy	AIFA
Latvia	State Medicines Pricing and Reimbursement Agency (SMPRA) under the Ministry of Health
Poland	Ministry of Health
Portugal	Infarmed
Romania	Ministry of Health
Slovakia	Ministry of Health
Slovenia	Medicines Agency – Public Agency of the Republic of Slovenia for Medicinal
Spain	Interministerial Committee for Pricing and Reimbursement (CIPM)
Egypt	Ministry of Health
Jordan	Jordan Food and Drug Administration (JFDA)
Kuwait	Ministry of Health
Lebanon	Ministry of Health
Qatar	Ministry of Health
Saudi Arabia	Saudi Food and Drug Authority (SFDA)
United Arab Emirates	Ministry of Health
Brazil	National Health Surveillance Agency (ANVISA)
Russia	Ministry of Health and Federal Antimonopoly Service
South Korea	The Health Insurance Review & Assessment Service (HIRA) and the National Health Insurance Service (NHIS)
Turkey	General Directorate of Pharmaceuticals and Pharmacies
South Africa	Pharmaceutical Economic Evaluations (PEE) Directorate

Sources: The authors, adapted from secondary and primary evidence

3.7 APPEALS BY STAKEHOLDERS TO REGULATOR DECISIONS

There is limited evidence on the presence of an appeals process for stakeholders. Information was only isolated in one country – the Czech Republic, where in June 2008 a newly implemented ERP system set maximum prices for 3,944 products. As a result, at the end of 2008, price cuts led to a number of appeals by industry due to distortion in price regulation (BMI Research, 2010).

Table 7: Presence of appeals process for stakeholders

Presence of appeals process for stakeholders	
Austria	✓
Belgium	✓
Bulgaria	✓
Czech Republic	✓
Estonia	×
France	×
Germany	✓
Greece	✓
Hungary	×
Italy	×
Latvia	✓
Poland	×
Portugal	✓
Romania	×
Slovakia	✓
Slovenia	✓
Spain	✓
Egypt	✓
Brazil	✓
Russia	×
Turkey	✓
South Africa	✓

Sources: The authors, adapted from secondary and primary evidence

3.8 NUMBER OF BASKET COUNTRIES

The number of countries in a basket, and the specific countries chosen, can have a significant impact on resulting drug prices (Houy and Jelovac, 2013) – a small number of reference countries could give significant weight to few countries whilst a large basket size can increase administrative difficulty without adding any value.

EU members generally elect to use a reference basket that contains 5 to 20 countries (Ruggeri and Nolte, 2013). Table 8 (adapted from Kanavos et al. (2010) and Toumi et al. (2014)) highlights the size of country baskets in European countries and the number of times each country is used as a reference in the basket of another country. Italy currently selects drug prices by referencing the largest number of EU countries, while it is referenced by only a limited number of reference countries (Austria, Belgium, France, Germany, Greece, Portugal and Spain). In recent years there has been a trend to increase the basket size (Houy and Jelovac, 2014), potentially as a means to reduce medicine prices further.

Austria expanded its basket of countries from 14 to 24 countries, while the Czech Republic used only 8 countries until 2009 (Leopold et al., 2012). In 2010, Greece increased its basket to 22 EU countries in order to reduce pharmaceutical prices and cut pharmaceutical expenditure due to the financial crisis. Other countries have also increased or have expressed interest in increasing the number of reference countries they use: Slovakia (from 8 countries in 2009 to all EU members) and Latvia (which is carrying out negotiations for the expansion of the number of reference countries used).

Germany, UK and France are the most referenced countries, because they launch drugs early and two of them (Germany, UK) employ free pricing methods for in-patent drugs (OECD, 2008).

3.8 FREQUENCY OF PRICE REVISIONS

Alongside the number, and choice, of countries, in the basket the frequency of price revisions can affect the prices derived using ERP. Many EU countries have a legal framework that calls for price renewals on a regular basis with regular intervals lasting from three months to five years (Rémuzat et al., 2015). Frequent price revisions may distort the role of the market, as they may reduce predictability and produce errors, especially when large baskets of countries are used (EFPIA, 2014). Nevertheless, the appropriate interval of price revisions depends on the respective national policy (European Commission, 2015) (See Table 10).

Table 8: Overview of baskets across countries

Countries with reference baskets	Countries acting as references																																				Basket size (countries)
	AUT	BEL	BGR	HRV	CYP	CZE	DNK	EST	FIN	FRA	DEU	GRC	HUN	ISR	ISL	IRL	ITA	LVA	LTU	LUX	MLT	MDA	NLD	NOR	POL	PRT	ROU	RUS	SRB	SVK	SVN	ESP	CHE	TUR	SWE	GBR	
AUT		■														■	■	■	■	■	■		■		■	■				■	■	■			■	■	24
BEL	■		■		■	■	■	■	■	■	■	■	■			■	■	■	■	■	■		■		■	■	■			■	■	■			■	■	26
BGR										■		■					■	■	■							■	■			■	■	■					10
HRV										■							■													■	■						3
CYP	■	■					■			■	■	■					■									■					■	■			■		10
CZE		■		■			■		■	■						■	■	■	■				■		■	■				■	■	■			■	■	17
DNK	■	■							■		■					■							■	■												■	9
EST													■					■	■																		3
FIN	■	■	■		■	■	■	■		■	■	■	■			■	■	■	■	■	■		■	■	■	■	■			■	■	■	■		■	■	28
FRA											■						■														■					■	4
DEU																																					0
GRC	■	■	■		■	■			■	■	■		■			■	■	■	■	■			■		■	■	■			■	■	■				■	22
HUN	■	■	■	■	■	■	■	■	■	■	■	■			■	■	■	■	■	■			■	■	■	■				■	■	■	■		■	■	29
ISR		■								■	■		■										■			■					■					■	8
ISL							■		■															■											■		4
IRL	■	■					■		■	■	■												■								■				■	9
ITA	■	■	■	■	■	■	■	■	■	■	■	■	■			■		■	■	■	■		■		■	■	■			■	■	■		■	■	27
LVA						■	■	■					■						■							■				■							7
LTU			■			■		■					■					■							■		■			■							8
LUX																																					0
MLT					■	■		■					■				■		■								■			■	■	■				■	11
MDA			■	■		■						■	■						■								■		■	■							9
NLD		■								■	■																									■	4
NOR	■	■					■		■		■					■							■												■	■	9
POL	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■		■	■		■	■			■	■	■	■		■	■	30
PRT										■																				■		■					3
ROU	■	■	■			■					■	■	■				■		■						■					■		■					12
RUS			■			■					■																					■					4
SRB				■													■														■						3
SVK	■	■	■	■	■	■	■	■	■	■	■	■	■			■	■	■	■	■	■		■		■	■	■				■	■			■	■	27
SVN	■									■	■																										3
ESP	■	■			■			■	■	■	■	■				■	■			■	■		■			■				■	■						16
CHE	■						■			■	■												■													■	6
TUR										■		■					■									■						■					5
SWE																																					0
GBR																																					0
Times country is in a basket	15	16	11	7	10	14	14	11	13	20	20	13	14	0	2	12	17	12	15	9	8	0	15	5	10	15	10	0	1	15	15	19	3	0	12	17	

Notes: [1]Belgium, the Czech Republic, Poland, Hungary, Denmark, Finland and Estonia are included as additional reference countries in case of non-availability of drug pricing data in other basket countries. [2]The Czech Republic and Spain contribute as alternatives in case of non-availability of drug pricing data in other basket countries. [3]Whilst Cyprus has an overall basket of 10 countries the actual price is based on a selection of countries from each of three sub baskets – high income (Denmark, Germany and Sweden); medium income (Austria, Belgium, France and Italy); and low income (Greece, Portugal and Spain).

Sources: The authors, adapted from secondary and primary evidence

3.9 CRITERIA FOR BASKET COUNTRY SELECTION

In terms of basket content, countries mainly take into account the following components to create a basket: (a) geographical characteristics, (b) financial similarity (Vogler et al., 2011), (c) availability of price data, (d) public health status and health insurance and (e) investment and contribution of pharmaceutical industry in financial performance (Critchley 2006).

There is limited information on the criteria that most countries use to choose their basket. Most EU countries use other EU members as references (OECD, 2008). For instance, the three Baltic countries (Estonia, Latvia and Lithuania) use each other in their reference baskets as they have common socioeconomics factors (Pudersell et al., 2007; Behmane et al., 2008), while northern and southern EU countries follow a similar trend (European Commission, 2015).

Table 9: Number of reference countries in basket across other non-EU countries

Countries	Number of reference countries of basket
Brazil[1]	9
Egypt	36 (and other optional)
Jordan	16
Kuwait	Country of origin
Lebanon	14
Qatar	Country of origin (and 2 optional)
Saudi Arabia	30
South Africa[2]	5
South Korea	7
United Arab Emirates[3]	31

Notes: [1]Brazil includes the following countries in the basket: USA, Canada, Portugal, Spain, France, Italy, Greece, New Zealand and Australia. [2]South Africa includes the following countries in the basket: Australia, New Zealand, Canada, Spain. [7]Prices are set to innovative drugs based on the ex-factory prices in seven industrialized countries (BMI Research, 2012). [3]Pricing is set at the median from referenced EU countries, the lowest price paid either in Saudi Arabia or the lowest price of an active pharmaceutical ingredient in the country of origin (BMI Research, 2015).

Sources: The authors, adapted from secondary and primary evidence

Table 10: Frequency of price revisions across the studied countries

Frequency of price revisions	
Austria	Two additional evaluations at six-month intervals, if reference prices were available in fewer than 12 EU Member States at the time of the initial evaluation; ad hoc revisions
Belgium	At launch only
Bulgaria	For reimbursed pharmaceuticals- every 6 months, For non-reimbursed- at launch only
Czech Republic	Annually
Estonia	For outpatient: on the basis of price agreement duration; For inpatient: once, annually
France	Every 4 to 5 years at product re-assessment
Germany	At launch only, at manufacturer's request and if new evidence becomes available
Greece	Biannual revision within four years of market entry
Hungary	At launch only
Italy	Ad-hoc and periodically depending on specific agreements
Latvia	Every two years
Poland	Ad-hoc and periodically in tiered intervals (every two, three, or five years)
Portugal	Annually
Romania	Annually
Slovakia	Twice per year
Slovenia	Twice per year
Spain	Every two years and ad hoc
Egypt	At launch, at manufacturer's request and on a random basis
Jordan	Every 2 years (plus four months after th reduction of prices in a reference country)
Kuwait	At launch only
Lebanon	Every 5 years
Qatar	At launch only
Brazil	At launch only
Russia	At manufacturers' request
South Africa	At manufacturers' request

Sources: The authors, adapted from secondary and primary evidence

Table 11: Criteria for basket selection across studied countries

Criteria for basket selection	
Austria	All EU countries
Belgium	Geographical proximity and comparable GDP levels
Bulgaria	Not well defined criteria; usually countries with similar GDP
Czech Republic	All EU countries
Estonia	Geographical proximity and comparable GDP levels
France	Geographical proximity and comparable GDP levels
Germany	Geographical proximity and comparable GDP levels
Greece	All EU countries
Hungary	Geographical proximity
Italy	ERP system is increasingly redundant
Latvia	Socioeconomic criteria
Poland	All EU countries
Portugal	The countries selected for the basket must have a similar per capita GDP to Portugal
Romania	No clear criteria are used to select basket countries
Slovakia	Geographical proximity
Slovenia	Geographical proximity
Spain	Countries where the medicines are available
Egypt	Geographical proximity, comparable GDP levels and the country of origin of the product
Lebanon	The price of an imported drug is based on the cost in the country of origin
Brazil	Countries with profile similar to Brazil
Russia	Countries with similar GPD per capita level and consideration of the country of origin
South Korea	South Korea does not specify the countries in the basket and decide on an ad-hoc basis
Turkey	Lowest in EU + geographical criteria
South Africa	Countries where prices are accessible and are regulated. Quality standards of countries also need to be similar.

Sources: The authors, adapted from secondary and primary evidence

Table 12: Price selection across countries

Type of comparator price used	
Austria	Ex-factory price
Belgium	Ex-factory price
Bulgaria	Ex-factory price
Czech Republic	Ex-factory price
Estonia	Ex-factory price
France	The starting point is the price claimed by the manufacturer; negotiation can use the ex-factory price
Germany	Retail price (NB: ERP as guidance)
Greece	Ex-factory price
Hungary	Ex-factory price
Italy	Ex-factory price
Latvia	Ex-factory price
Poland	Ex-factory price
Portugal	Ex-factory price
Romania	Ex-factory price
Slovakia	Ex-factory price
Slovenia	Ex-factory price
Spain	Ex-factory price
Egypt	Retail price
Jordan	Ex-factory price
Lebanon	Wholesale price
Saudi Arabia	Ex-factory price
United Arab Emirates	Wholesale price
Brazil	Ex-factory price
Russia	Wholesale and retail price
South Korea	Ex-factory price
Turkey	Ex-factory price
South Africa	Ex-factory price

Sources: The authors, adapted from secondary and primary evidence

Table 13: Method for calculation of reference price across countries

Method of calculation of reference price	
Austria	Average across basket
Belgium	Average across basket
Bulgaria	Lowest price in basket
Czech Republic	Average of the three lowest prices in basket
Estonia	Price cannot exceed the highest price in the basket
France	"Prices similar to reference countries and not lower than the lowest price"
Germany	Weighted based on market size and purchasing power parity
Greece	Average of the three lowest prices in basket
Hungary	Lowest price in basket
Italy	Average across basket
Latvia	Third lowest price among Denmark, Czech Republic, Romania, Slovakia and Hungary
Poland	Lowest price in basket
Portugal	Follows different calculation methods depending on the sector. Outpatient: country average, Inpatient: lowest price
Romania	Lowest price in basket
Slovakia	Average of the three lowest prices in basket
Slovenia	Lowest price in basket
Spain	Lowest price in basket
Egypt	Lowest price in basket
Jordan	Average across basket
Lebanon	The price of an imported drug is based on the cost in the country of origin. Final price needs to be lower than one of the following: (i) The ex-factory price in the country of origin. (ii) Import prices charged for the same brand in seven countries in the Middle East.(iii) The median manufacturers' price in seven European countries, or (iv) The import price of similar drugs that are already marketed in Lebanon.
Saudi Arabia	Lowest price in basket
United Arab Emirates	Lowest price in basket
Brazil	Lowest price in basket
Russia	Lowest price in basket
South Korea	Average across basket
Turkey	Lowest price in basket
South Africa	Lowest price in basket

Sources: The authors, adapted from secondary and primary evidence

3.10 TYPE OF COMPARATOR PRICE USED IN ERP

Most European countries have used ex-factory prices in their international comparisons (Kalo et al., 2015), because this method helps to minimize price deviations that may arise due to differences in distribution mark-ups (Nguyen et al, 2015). The implementation of ERP using the ex-factory price is considered to be more suitable than other methods, for example, using the wholesale price, as distribution margins and tax rates are different across countries leading to difficulties in international comparisons (EFPIA, 2014). However, there are some countries that use the wholesale price and some that use the pharmacy retail price (Espin et al., 2014) (see Table 12). ERP is generally based on officially published prices. Since price negotiations and discounts are kept confidential within a country most countries will be using reference prices that may be higher than the negotiated price enjoyed in the reference country.

3.11 METHODS FOR CALCULATION OF THE REFERENCE PRICE

Generally, the most preferred method of reference price calculation is the use of an average formula (Gandjour, 2013) although there are other mechanisms in use, such as using the average of the *n* lowest or the lowest price in the basket. (European Commission, 2015). In the countries studied in this paper using a lowest price based calculation is the most common (Table 13), against the recommendation of EFPIA (2014) which states that an average price be used to enhance fairness. According to our results, some countries may include more than one criterion to set the reference price of a product, while other members may not refer to the selected method officially.

3.12 SOURCES OF INFORMATION FOR PRICING DECISIONS

The implementation of ERP requires access to price information and according to EFPIA (2014), this data should be publicly available and reliable. Non-availability, price heterogeneity, non-reliability and a lack of transparency can reduce the effectiveness of ERP (Rémuzat et al., 2015). Many countries support free access to price data, although the extent that

different stakeholders contribute to the accessibility of information varies across countries (see Table 14). Generally, in EU countries the necessary price data is provided by the marketing authorization holder (i.e. the manufacturer) (European Commission, 2015).

3.13 INCLUSION OF WEALTH ADJUSTMENTS IN ERP CALCULATIONS

Whilst most countries reference those with similar economic criteria there are situations where countries reference those with a higher GDP – for example Bulgaria, with a GDP of $7929 (per capita) referencing France, Spain and Italy (European Commission 2015). In such situations, countries can account for differences in GDP by making wealth adjustments based on Purchasing Power Parity (PPP) or GDP growth. Despite this possibility, evidence shows that none of the studied countries perform such adjustments meaning that countries referencing those with higher GDP than themselves may be exposed to artificially high prices and vice versa. Germany reports that a formal weighting of prices by the estimated yearly turnover of a pharmaceutical and PPP of other countries could be applied, although whether or not this has ever been implemented is unknown.

3.14 ACCOUNTING FOR EXCHANGE RATE FLUCTUATIONS

Similarly, if countries reference those with different currencies then exchange rate fluctuations can influence the calculated reference price (Kanavos et al., 2010). If weaker currencies and / or poorer countries are used in the reference basket, a downward adjustment is usually seen as exchange rates are used to contain prices. In Estonia, valid exchange rates are taken into account in the price calculation (Pudersell et al., 2007). In the Czech Republic, price estimation is based on the average exchange rates for the three months prior to the review (BMI Research, 2010) and in Jordan, exchange rates are taken into account due to possible price changes (BMI Research, 2015). In Turkey, which references EU countries using the Euro, reference prices are converted to 70% of the previous year's average exchange rate between the euro and the Turkish lira (BMI Research, 2016). In contrast Saudi Arabia is one of many countries that does not

Table 14: Sources of information across countries

Sources of information for pricing decisions	
Austria	Manufacturers
Belgium	Manufacturers and public information sources (e.g. websites)
Bulgaria	Access to confidential pricing information – EURIPID
Czech Republic	Manufacturers and public information sources (e.g. websites)
Estonia	Manufacturers and public information sources (e.g. websites) and access to confidential pricing information
France	Public information sources (e.g. websites)
Germany	Manufacturers and public information sources (e.g. websites)
Greece	Manufacturers and public information sources (e.g. websites) and access to confidential pricing information
Hungary	Public information sources (e.g. websites) and access to confidential pricing information
Italy	Manufacturers and public information sources (websites)
Latvia	Manufacturers
Poland	Manufacturers and access to confidential pricing information
Portugal	Manufacturers and public information sources (websites)
Romania	Manufacturers
Slovakia	Public information sources (e.g. websites)
Slovenia	Public information & confidential sources (websites)
Spain	Access to confidential pricing information
Egypt	Manufacturers and public information sources (e.g. websites) and access to confidential pricing information
Jordan	Manufacturers
Lebanon	Manufacturers and public information sources (e.g. websites)
United Arab Emirates	Manufacturers and public information sources (e.g. websites)
Brazil	Currently price database via UNASUR in the media
Russia	Manufacturers and public information sources (e.g. websites) and access to confidential pricing information
Turkey	National Authorities of reference countries (public info)
South Africa	Manufacturers and public information sources (e.g. websites) and access to confidential pricing information

Sources: The authors, adapted from secondary and primary evidence

Table 15: Inclusion of wealth adjustments in ERP calculation

Inclusion of wealth adjustments	
Austria	×
Belgium	×
Bulgaria	×
Czech Republic	×
Estonia	×
France	×
Germany	×
Greece	×
Hungary	×
Italy	×
Latvia	×
Poland	×
Portugal	×
Romania	×
Slovakia	×
Slovenia	Used to be (85% of ERP)
Spain	Indirectly through Eurozone basket
Egypt	×
Jordan	×
Kuwait	×
Lebanon	×
Qatar	×
Saudi Arabia	×
United Arab Emirates	×
Brazil	×
Russia	×
South Korea	×
Turkey	×

Sources: The authors, adapted from secondary and primary evidence

Table 16: Methods for dealing with exchange rate fluctuations

Methods for dealing with exchange rate fluctuations	
Bulgaria	✓(Fixed exchange rate)
Czech Republic	✓(Average exchange rates for the three months prior to the review)
Estonia	✓(Spot exchange rate)
France	✓(Use simple currency countries)
Germany	✓(Prices based on PPP provided by Eurostat)
Greece	✓(Spot exchange rate)
Hungary	✓(Moving average of previous 3 months)
Latvia	✓(Moving average of previous 60 days)
Poland	✓(Monthly average rate of the Polish National Bank for the month prior to submission)
Romania	✓(Quest III methodology is used to establish the RON – Euro exchange rate)
Slovakia	✓(Moving average of previous 12 months)
Spain	✓(Fixed exchange rate)
Egypt	✓(Use the exchange rate at the time when the pricing decision is made)
Jordan	✓(Use moving average of the previous month)
Brazil	✓(Moving average of previous 60 days)
Russia	✓(Spot exchange rate)
Turkey	✓(Reference prices will be converted at 70% of the previous year's average exchange rate between the euro and the Turkish lira)
South Africa	✓(Moving average of previous years)

Sources: The authors, adapted from secondary and primary evidence

consider exchange rates in price determination (BMI Research, 2016). Some countries in the Eurozone, notably Spain, have moved to using Euro only countries in their reference basket to avoid multiple currencies and decrease price parities.

3.15 LINK BETWEEN PRICE AND REIMBURSEMENT

ERP can be aligned with the reimbursement processes to contribute to price reduction (Kanavos et al., 2010) (Table 17). Concerns arise from the determination of reimbursement prices using ERP. These concerns centre around the "appropriateness" of chosen reference countries (for example, countries with higher levels of GDP or bigger markets), and the confidentiality of negotiated prices in the reference countries (BMI Research, 2016). In Slovenia the introduction of ERP is an additional tool to improve the drug reimbursement system (Albreht et al., 2009). In 2011, Slovakia introduced pharmacoeconomic analysis of publicly reimbursed drugs to control pharmaceutical expenditure in parallel to international price comparisons (BMI Research, 2012).

3.16 INTERACTION OF ERP WITH HTA AND VBP

ERP implementation can limit the ability of other methods to regulate drug pricing (Koh et al., 2016) and any combination of approaches can present difficulties when determining the most effective pricing policy. ERP does not take into account the role of VBP, which is related to the contribution of drugs to patients' health and society (EFPIA, 2014). This is because ERP is often thought of as a more technical and administratively complex process than VBP, due to the requirements of large amounts of price data (Vogler et al., 2014). In addition, the value of drugs, which is considered under VBP, can differ across countries (Paris and Belloni, 2013). The alignment of the two methods is complex as price determination should be based on value, which is subject to various assessments (Toumi et al., 2014).

As far as price setting based on HTA recommendations is concerned, its inefficient implementation may lead to ERP use, ultimately aiming to contribute to drug spending control. The final assessment of HTA and the outcomes of cost-effectiveness analysis (which are supposed to reflect willingness to pay of society) may not be taken into account due to the parallel use of international comparisons (Koh et al., 2016).

3.17 ERP ALIGNMENT WITH OTHER NEGOTIATION TOOLS OF REIMBURSEMENT

The use of ERP can facilitate the negotiation and reimbursement processes (WHO, 2015). It is generally seen as one of the criteria used in price negotiations, with other factors including issues such as R&D expenditure (Gandjour, 2013). In Italy and Estonia, pricing negotiations and the reimbursement process are based on a combination of ERP and internal reference pricing (Martini et al., 2007; Pudersell et al., 2007). In France and Spain, ERP operates as a significant method in negotiations between authorities and industry for innovative drugs of high therapeutic value (Ruggeri and Nolte, 2013) (Table 17).

In the Czech Republic, EU prices and the following criteria are evaluated for negotiation and reimbursement purposes: clinical efficacy, reference prices, budget impact and a form of cost-effectiveness analysis (Kanavos et al., 2010). Countries and health authorities may apply some informal evaluation methods for reimbursement, while other governments can use different ERP designs to enhance negotiations with the in-patent drug industry (Europe Economics, 2013; Espin et al., 2014).

3.18 LINK BETWEEN ERP REGULATION AND PATENT STATUS

Countries should take into account the value of innovation in ERP design. Drug authorization and patent-expiry vary across countries and thus the same product can be in-patent in one country and off-patent in another at the same time. In most cases, when a drug loses patent protection the price is reduced compared to its in-patent price. Therefore, it is possible that a country where the drug is still in-patent is using reference prices from a country where the drug has lost its patent protection and is therefore cheaper. This could lead to artificially low prices in the referencing country which could lead to spillover effects such as parallel trade. Evidence in the literature on whether ERP respects the patent status is scarce to non-existent, however, it has been recorded that the Czech Republic does not take into consideration the patent protection status in the comparison of drugs (BMI Research, 2014) which was confirmed in the stakeholder questionnaires. Estonia, Portugal, Slovakia, Egypt, Brazil and Russia have also been reported to take the cheaper or generic product price to inform their basket (Table 17).

Table 17: ERP relationship with other pricing and reimbursement policies

	Link between price and reimbursement	Interactions between ERP and HTA/VBP	Alignment with other reimbursement & negotiation tools	Link between ERP and patent status
Austria	✓	Results of HTA are not systematically incorporated into public decision-making	Despite ERP, there are financial arrangements with manufacturers	
Belgium	×	There is no interaction between HTA and ERP	"Given the artificial nature of the list prices, ERP is not useful to use in price negotiations."	✓- Takes the originator brand to inform our basket
Bulgaria	✓	HTA is performed before ERP setting. HTA serves as a basis for approval of the list price and reimbursement price.	No, but discount agreements for innovative drugs are contracted annually	✓- Takes the originator brand to inform our basket
Czech Republic	✓	Pricing: ERP; Reimbursement: ERP with other criteria, incl. HTA	ERP as a negotiation tool for innovative drugs	×- Takes the cheaper product/generic product to inform our basket
Estonia	✓	ERP and HTA are not directly linked. When the price is calculated based on the HTA, the price is compared with prices within the basket and cannot exceed the highest one.	ERP is one tool for setting a fair price of a pharmaceutical. However cost-effective price, internal reference price and RSA have a bigger impact during the negation process.	×- Takes the cheaper product/generic product to inform our basket
France	✓	Interaction between HTA and ERP during the negotiation process of pharmaceuticals with an ASMR I-III.	ERP as a negotiation tool for innovative drugs	✓- Takes the originator brand to inform our basket
Germany	✓	Both information from HTA and ERP are used to inform the price negotiation process (if there is added value of the new product)	ERP as guidance for price negotiation if needed	
Greece	✓	Critical for pricing/reimbursement; used with clawbacks/rebates	"ERP reflects the maximum price that the system could reimburse, adjusted downwards by rebates and discounts."	
Hungary	✓	There is no link between HTA and ERP. The ERP originated from HTA cannot be higher than the lowest price in Europe.	"First criteria of negotiation is to be in line with the legal regulation of ERP-requirements. All the other tools can be used afterward."	✓- Takes the originator brand to inform our basket
Italy	✓	The role of ERP is marginal in the Italian setting; used as a criterion to guide negotiations	ERP and Internal Reference Pricing	
Latvia	✓	Pricing: ERP: Reimbursement: other criteria, incl. HTA		
Poland	(✓)	The price negotiations are carried out after the HTA process	"Price comparison used a negotiation tool particularly when lower prices are available in more wealthy countries"	
Portugal	✓	ERP is used to fix ex-M price of outpatient medicines; For inpatient, ERP is used in the negotiation process along with the HTA decision	HTA process is followed by negotiation and results in financial RSA	×

Table 17 continued: ERP relationship with other pricing and reimbursement policies

	Link between price and reimbursement	Interactions between ERP and HTA/VBP	Alignment with other reimbursement & negotiation tools	Link between ERP and patent status
Romania	✓	ERP can influence the estimated budget impact of a new reimbursed drug, which is one of the criteria considered in the Romanian HTA scorecard; critical for pricing/ reimbursement	Negotiation takes places at Insurance House level & is combined with RSAs; as of end-2016, there were only a handful of RSAs	✓- Takes the originator brand to inform our basket
Slovakia	✓	HTA mandatory requirement since 2011 (CEA/CMA plus BIA)	"For some highly innovative medicines for which, there are no alternatives in the market, they can be reimbursed through PAS"	×- Takes the cheaper product/generic product to inform our basket
Slovenia	×	Some HTA performed at basic level despite the initiatives put forward by the NIPH		
Spain	✓	ERP is used as another criterion for pricing, jointly with efficacy and budget impact analysis	ERP as a negotiation tool for innovative drugs	✓- Takes the originator brand to inform our basket
Egypt	✓	Critical for pricing/reimbursement	"ERP plays a major role in the negotiations to get an even lower price than lowest one"	×- Takes the cheaper product /generic product to inform our basket
Jordan		Critical for pricing/reimbursement		
Kuwait		Critical for pricing/reimbursement		
Lebanon		Critical for pricing/reimbursement		
Qatar		Critical for pricing/reimbursement		
Saudi Arabia		Critical for pricing/reimbursement		
United Arab Emirates		Critical for pricing/reimbursement		
Brazil	✓	List price via ERP is the starting point for discounts for the public system, SUS. Negotiation between HTA Committee (CONITEC) and companies reduces the ERP prices	"As explained to SUS, discounts applied to the public system after ERP."	×- Takes the cheaper product /generic product to inform our basket
Russia	✓	N/A		×- Takes the cheaper product /generic product to inform our basket
South Korea		HIRA uses economic evaluation to influence the pricing of drugs and medical devices, the formulary listing and the benefit package		
Turkey	✓	Critical for P&R; extensive discounting for reimbursement		
South Africa	The ERP process results in the final list price. The decision to reimburse is taken independently.	N/A		✓- Takes the originator brand to inform our basket

Sources: The authors, adapted from secondary and primary evidence

4. DISCUSSION & POLICY IMPLICATIONS

The objective of this paper was to analyse ERP implementation in different geographical jurisdictions and to determine levels of interaction between ERP and other pricing and/or reimbursement policies. A systematic literature review was conducted in order to record the variations in ERP implementation across a set of countries. Specific endpoints were set to capture the major ERP salient features. The findings of this review are discussed in this section. An additional paper in this series analyses the consequences that these variations may have within and across countries (Kanavos *et al.,* 2017). Moreover, a set of policy options, which could be followed by governments in order to achieve a transparent, simple, stable and sustainable ERP system, are presented.

According to the systematic literature review all 29 countries of interest in this report have, at one point or another, implemented ERP, either as a major or supportive pricing process, to set or inform pharmaceutical prices.

ERP has been widely used across our sample as a cost-containment tool as well as a price control method. For instance, Greece, Slovenia and Turkey introduced ERP to reduce and control drug expenditure, while Russia, Latvia, Bulgaria and Spain promoted international comparisons to regulate prices and attain lower level of prices.

In several countries including Hungary and Italy, ERP is not only implemented in the pricing decision, but it is also aligned with the reimbursement process to contribute to further price reductions.

Reimbursable and in-patent drugs are predominantly subject to ERP in order to control reimbursement prices. However, evidence from the systematic literature review shows that numerous countries such as Austria, Bulgaria, Jordan, Portugal and many others, use ERP in products regardless of their patent status whilst Belgium, Jordan and Romania use ERP for all medicines, regardless of their inclusion on the national positive list and resulting reimbursement.

The majority of countries use ERP as their main pricing method with implementation taking a formal or informal role. 16 of the studied countries (including the Czech Republic, Slovenia and Greece) use international comparisons as a core pharmaceutical pricing method, while others (i.e. Germany) use ERP in specific medicines (i.e. vaccines). When ERP implementation is informal, as in Italy and Russia, foreign prices may be used unofficially either to set prices of pharmaceuticals or facilitate the negotiations between the competent authority and drug manufacturers. As a result, many countries do not explicitly define the role that ERP plays in their pricing mechanisms.

The transparency of ERP processes also varies between countries. Many countries, including Austria, Portugal and Russia, have defined legislative and well-established frameworks, while others – Bulgaria and Italy – present less straightforward, less transparent processes. Variations have further been observed in the authority responsible for the implementation of ERP. In a few countries, such as Lebanon, Russia, Slovakia and UAE, ERP lies in the jurisdiction of the Ministry of Health. While, in the majority of the studied countries, ERP is implemented by pricing committees or medicines associations.

Significant heterogeneity across our sample was observed in the number of the countries and the countries included in the ERP basket. According to the latest available data, ten countries out of the 29 of interest here have a large basket of 20 or more reference countries. Only five countries (the Czech Republic, Spain, Romania, Jordan and Lebanon) out of the 29 have a medium-sized basket of 12-17 reference countries. 12 countries across our sample have a small basket of up to ten reference countries. Despite the majority of countries using a small basket there has been a recent trend to increase the size of the basket. Examples of this trend were drawn from Austria, the Czech Republic, Greece, Latvia and Slovakia.

Reference country selection, generally influenced by financial and geographic characteristics, data availability, public health status and the role of industry in the country in question, is a key component of an ERP system. Despite is importance there is limited data highlighting the reasons behind basket country choice, over and above information on Estonia, Latvia and Lithuania, which tend to include countries with common socioeconomics factors in the selection of their basket. Many Northern and Southern EU countries also follow a similar trend (European Commission, 2015). Based on our findings Germany, the UK and France are the

most referenced countries among European and some non-EU countries.

In the countries studied in this paper, using a lowest price based calculation is the most common method to calculate the reference price. According to the latest available literature, 16 of the countries use the lowest price in the basket to derive the ERP. The Czech Republic, Greece and Slovakia use the *n* lowest of the basket as an alternative to calculate their prices. Whereas, South Korea, Austria, Portugal and Belgium use the average price across the reference basket.

Evidence on the frequency of price renewals across the studied countries, was limited and drawn from ten countries. Portugal and Romania revise their prices annually, whereas Jordan and Latvia revise it biannually.

Despite the fact that the majority of countries reference the ex-factory price, there is evidence that shows that ex-factory prices do not incorporate any confidential discounts and rebates negotiated between payers and manufactures. As a result, it is common for referenced prices to not reflect reality, which can lead to artificially inflated prices in some countries. Similarly, countries tend not to account for dynamic changes in exchange rates or reference country wealth differences, based on GDP or PPP. Consequently, countries referencing those with higher GDP, such as Bulgaria, may be exposing themselves to artificially high prices, counteracting the general objective of ERP systems.

Whilst ERP can be used in isolation, it can also be used in combination with other processes, such as HTA or VBP. Evidence on the interactions of ERP with other pricing regulations such as HTA or VBP is limited within the studied literature. The incorporation of ERP with additional tools for negotiation and reimbursement can improve access to medicines over and above price cuts. Italy, Estonia, France, Spain and the Czech Republic are examples of countries where ERP serves as part of the negotiation process in the final pricing decision of pharmaceuticals. Finally, evidence in the literature on whether ERP respects the patent status is scarce to non-existent, however, it has been recorded that the Czech Republic does not take into consideration the patent protection status when calculating the reference price using the basket. Estonia, Portugal, Slovakia, Egypt, Brazil and Russia have also been reported to take the cheaper or generic product price to inform their basket.

Our results have highlighted substantial heterogeneity in the design of ERP systems between countries. Such variations may be the result of the different health system policy objectives in individual countries, differing health requirements, different working budgets, and different pricing policies. Differences in the perception of value of innovation and of the importance of R&D may also result in such variations in the ERP design.

The disparities seen in ERP design across countries can translate into effects on the pricing system. ERP, if implemented without alignment with public policy objectives, may influence the price levels of pharmaceuticals resulting in inflated prices in low-income countries, jeopardizing their availability and affordability and leading to reduced incentives for continued R&D.

These issues are the result of "path dependence", for which ERP has been criticized, i.e. the features of the ERP system influence the overall outcome achieved (Leopold et al. 2012, Kanavos et al. 2010 and Rémuzat et al. 2015). For instance regular price revisions can lead to greater short-term cost-containment, due to lower price levels in a country. The level of price reduction also depends on the countries selected for the basket and the price considered in the basket.

In a simulation exercise by the European Commission in 2015, it was shown that more frequent price revisions resulted in higher healthcare savings. In this scenario, the European Commission tested the extent of the price reduction if all countries re-evaluated their prices every six months. This resulted in a decrease of about 6% on the average medicine price in all 28 European Countries (European Commission 2015). Frequent price revisions, combined with exchange rate fluctuations, can impact prices in a downward manner, and result in higher savings.

In addition, in Slovakia, ERP tended to result in higher prices relative to neighboring countries, with similar income levels, due to basket country selection. This is because the German price and the price of the originator country of the pharmaceutical are used to calculate the Slovakian reference price, Germany

tends to have relatively high ex-manufacturer prices and the country of manufacture tends to be a high-priced country, given the production costs. However, due to an ERP policy change in 2009, Slovakia lowered prices by calculating the reference price using the mean of the six lowest price countries within Europe (Kalo et al. 2008, Leopold et al. 2012).

The way in which ERP is implemented in a country might have an additional impact on the availability of pharmaceuticals in that country. This is due to ERP policies, which are most likely to take place in highly regulated and/or small markets. Markets with flexibility on pricing, or markets that are large in size, with higher GDP, increased public healthcare spending, a higher percentage of GDP on health expenditure and a higher price level of pharmaceuticals are less likely to suffer from reduced availability (Håkonsen et al. 2009; Espin et al. 2014). For example, out of 15 European countries, Germany, where pricing is not regulated at ex-factory level, had the highest pharmaceutical prices and availability (Leopold, Mantel et al. 2012). Other examples include Slovakia, where a change in its reference country basket to include all EU Member states resulted in companies disregarding the newly implemented prices or lobbying for exemptions of their products, leading to access delays (Leopold, Vogler et al. 2012).

Over and above the impact of ERP design within a country discussed above, the policy can have cross-border spillover effects. These include price instability, launch delays, unwillingness of manufacturers to launch in low price countries and price convergence towards the international average. For example, the frequency of price revisions is an important driver of price change over time when applying ERP. Yearly systematic price revisions can lead to faster price reductions when compared to revisions taking place every three years. Thus, increasing the frequency of price revisions will contribute to decreasing the overall pharmaceutical prices which can cause price erosion (Toumi et al. 2014).

Finally, ERP design determines whether price convergence results in higher or lower prices. Larger baskets, and an increase in basket size over time, are associated with some price convergence between European pharmaceutical prices (Leopold et al. 2012, BMI Germany 2011 and Houy and Jelovac, 2014). It has also been argued that ERP can lead to a downward price convergence in Europe when the lowest price in the country basket rather than the average price is used to calculate the reference price (Toumi et al. 2014).

In general, whilst there is convergence towards the mean there is no evidence that this is upwards. Importantly, if countries implementing ERP use the lowest, or the average of the lowest, of the basket one can hypothesis that any convergence seen will appear to be downwards as the mean will also decline.

4.1 POLICY IMPLICATIONS

Our systematic literature review revealed significant heterogeneity in the ERP processes used in the countries of interest. There are a number of policy implications resulting from some of the potentially suboptimal practices included in certain ERP systems such as launch delays in low-income countries, parallel trade reducing drug stock levels, inflated prices in low-income countries, globally declining pharmaceutical prices, reduced incentive for continued R&D and reduced access to medicines in some regions. During the design phase of ERP governments are likely to focus on the short-term financial gains that could be the result of a newly implemented ERP system that uses a "lowest price in the basket" style calculation. However, such decisions could negatively impact healthcare systems in the long term. Whilst it may be difficult to please all stakeholders a number of ideas have been presented for approaching the issue of heterogeneity in a non-partisan, systematic way (Sullivan et al, 2017). These key principles, which make up an "ideal" ERP system, are presented below. They are organized into four sections. (i) Objectives and Scope of External Price Referencing Systems, (ii) Administration and Operations, (iii) Methods for the Conduct of External Price Referencing, and (iv) Implementation of External Price Referencing. We assessed the 29 countries of interest for their adherence to these best practice principles. A discussion around this assessment is given after a description of each principle:

4.1.1 Objectives and scope of external price referencing system

External price referencing system objectives should be clear and align with country specific health system objectives

Outlining the objectives and scope is an important first step in designing an ERP system. They should be contained within a scoping document, should be legislated and routinely reassessed. Health system goals should also be considered so that the ERP system functions cohesively within the health system and does not focus too narrowly or short-term. Mechanisms should be developed for monitoring the ERP system in order to ensure that target prices are selected and used in accordance with the guiding objectives.

External price referencing systems should focus on in-patent products considered for the purposes of coverage, pricing and reimbursement decisions

Without external controls, the relative lack of competitive forces for newly launched, in-patent pharmaceutical products can result in exorbitant prices. With this in mind, ERP is most appropriately applied to in-patent medications. Off-patent medications are naturally subject to greater competitive forces, which drive down prices. In addition, there are other mechanisms available for directly or indirectly regulating prices of off-patent medications, such as price capping or internal price referencing, the latter being used extensively to set a price ceiling on reimbursement.

Prices developed using ERP should not override conclusions of health technology assessment (HTA) or value-based pricing approaches

Several countries utilize ERP as an adjunct to explicit methods of value assessment, such as formal cost-effectiveness analysis. In principle using multiple approaches should be encouraged. However, some approaches, such as HTA and value-based pricing systems, have a stronger theoretical underpinning, in that they directly consider the overall value of a pharmaceutical agent to a population in order to make coverage decisions and determine prices. By contrast, ERP systems rely on prices set in other countries, often using unknown pricing mechanisms and methodologies. Therefore, ERP-based prices should not override those developed via other more robust evidence-based approaches, if they disagree. Further, final prices should align with conclusions regarding the value of the product to the population. Overall, countries might expect to pay more for products providing greater benefit, even if ERP results contradict this.

4.1.2 Administration and operations

The ERP system should have administrative simplicity and transparency

Ensuring administrative simplicity and transparency is important for several reasons. First, systems with these characteristics are easier to manage, which means that fewer resources will be required in order to establish and maintain them. Second, these features allow all relevant stakeholders to anticipate pricing decisions. This is also important for suppliers of pharmaceuticals in terms of obtaining clarity in each market they operate in. Uncertainty surrounding pricing mechanisms may cause suppliers to delay or even prevent entry into certain countries. In addition, price negotiations will likely be more straightforward if all parties concerned clearly understand the country's pricing mechanisms, especially if these prices are strictly enforced. When deviations from the typical pricing procedures occur, the rationale should be documented and made publicly available. Finally, simple, transparent systems are less prone to corruption and are easier to audit in order to promote efficiency.

Stakeholders should participate in the design and review of the ERP system

Stakeholders representing a wide variety of interests, including industry, patients, health care professionals and academic experts, should be consulted in the design of the ERP system. At a minimum, stakeholder feedback should be elicited on the scoping document or the draft legislation. Involving a variety of stakeholders can result in a system that best balances the needs and concerns of all groups involved. It can also lead to greater transparency and decreased uncertainty. Any changes made to the ERP system and scoping document should incorporate stakeholder recommendations, and periodic input from these groups should be requested, to ensure that the system remains relevant.

Stakeholders should be able to appeal regulator decisions

Regulators should develop a process and provide opportunities for stakeholders to appeal pricing decisions made explicitly using ERP. Allowing for appeals is essential, given the inherent uncertainty in prices developed via ERP. For example, referenced prices may not reflect actual transaction prices, and referenced countries often use unknown methods of arriving at a given price. The appeals process may also illuminate issues with the ERP system's design or management and will allow extenuating circumstances to be presented and considered. Appeals should be documented, the process should be straightforward, stakeholders must be aware of the requirements of the process, and timelines should be finite.

Reference countries should be selected based on similarities in economic status and health system objectives

Selecting reference countries with a similar economic status and health system objectives increases the likelihood of arriving at appropriate price levels, which align with other healthcare decisions made within the country. Demanding the same price in lower-priced markets as in higher income markets could cause innovative pharmaceuticals to become prohibitively expensive for developing countries. In addition, heavily referencing lower-income countries could lead pharmaceutical companies to delay launches in those countries. If lower-income countries reference prices in higher-income countries, where more sophisticated methods such as HTA are used for determining value and pricing, prices can be adjusted, for example, using purchasing power parity (PPP) exchange rates, or through a per capita income adjustment indicator.

International implications of ERP implementation should be considered

The wide use of ERP often has a number of unintended consequences internationally, which may directly or indirectly affect members of the broader stakeholder community. Worldwide decreases in drug prices may lead to decreases in research and development of new products. The value of pharmaceutical innovation to the healthcare system should always be considered and reflected in drug prices which will require systems to consider the international implications of their pricing policies.

4.1.3 Methods for the conduct of external price referencing

Publicly available ex-factory prices should form the basis of the ERP system

Ex-factory prices are most reflective of actual transaction prices compared to other prices, such as the retail price, which incorporates additional costs, vary across countries (e.g. wholesaler costs, pharmacy service fees and taxes) and are subject to national regulatory practices. Using publicly available sources to locate price information is ideal because it encourages transparency, though this information is not always available for all countries. Manufacturers and audit systems should provide alternative sources of information, when prices are not publicly available. Countries should consider incorporating multiple mechanisms for setting target prices so that information deficiencies do not delay price negotiations, as well as set time limits for the pricing processes to be completed.

The mean of prices in reference countries should be used

Currently, most ERP systems use the mean, median or minimum price of referenced countries when developing a national target price. Assuming that reference country selection is based on similar economic status and health system objectives, using the minimum price is generally not appropriate, since countries with the lowest prices may have unusual public health or economic circumstances, which could justify a lower price. Therefore, an average price rule should form the basis of ERP systems with the median being used if outliers are a concern. If prices are not available in all reference countries price setting should proceed based on available information. Including more countries in the reference basket increases the likelihood of selecting a reasonable price while ensuring information availability.

Patent status should be respected

When determining target prices for in-patent products, whose patents may have expired in one or more reference countries, referring to prices of off-patent medications within the reference countries should be avoided. Patents provide necessary intellectual property protections for pharmaceutical companies by rewarding past research and

development efforts while encouraging future investments. In addition, ignoring patent protections may lead companies to avoid launching in certain markets, which would decrease access in those regions.

ERP formula should avoid the impact of exchange rate volatility

Exchange rates can vary dramatically over time, so using an exchange rate at a single time point may result in unstable or perverse price estimates. Employing techniques to decrease the impact of this volatility on the estimated price, such as using a moving average of the exchange rate, is suggested. Countries within the European Economic and Monetary Union (EMU) could also consider excluding non-euro currencies, which tend to be more volatile. Exchange rates do not completely adjust for the purchasing power of a given currency, which can vary even when referencing countries of a similar economic status. To address this issue, countries could consider using purchasing power parity (PPP) exchange rates or adjusting prices to per capita wealth levels in the actual country compared with its comparators.

4.1.4 Implementation of external price referencing

Price revisions should be kept to a minimum and should be carried out consistently to avoid the perception of opportunistic behavior

Price revisions should occur on an infrequent but scheduled basis and the schedule should be made public to ensure transparency and fairness. Typically, price comparisons would take place at launch, and price revisions could take place perhaps once or twice annually in order to ensure stability and administrative simplicity. Such an approach decreases uncertainty, while assuring a level of stability and predictability. It also prevents regulators from strategically adjusting prices, dependent upon the launch schedules of particular pharmaceutical agents.

ERP-based prices should be aligned with other tools used when negotiating reimbursement

Many countries utilize price setting through ERP as an adjunct to other methods of value determination and risk management. Therefore, ERPs relative importance in defining list prices varies. When negotiating reimbursement, insurers sometimes enter into managed entry agreements, wherein they agree with a manufacturer to share in the financial risk of introducing a new pharmaceutical agent into a given market. Such agreements are confidential in nature and can a take a number of forms, such as price-volume agreements, coverage with evidence development or outcome guarantees. Countries entering into these arrangements will need to consider how the prices developed using ERP align with such agreements. Countries with value-based pricing systems should proceed with caution in their thinking about introducing ERP, since potential reference countries may not be establishing prices based on product value. Additionally, other pricing tools can facilitate the implementation of differential pricing and, consequently, improve patient access to in-patent medicines in lower income countries. In all cases where ERP is used alongside other methods of price and value determination, the relative importance of ERP in establishing prices should be critically considered.

4.2 COUNTRY ADHERENCE TO 14 BEST PRACTICE PRINCIPLES

Using the latest evidence drawn from the systematic literature review and the results from primary data collection, we analysed the extent to which the 29 countries of interest followed the 14 best practice principles (See Table 18). None of the countries in question seemed to follow all 14 of the principles with most failing to use the mean price of the basket and an administratively simple and transparent system which involved stakeholder participation. Most countries use the lowest price in the basket, or the average of the lowest *n* prices, have large baskets, reducing administrative simplicity. Similarly, whilst external stakeholders may be consulted, their contribution to the actual decision making related to ERP is practically null, it is an administratively driven process that excludes active participation by stakeholders. Belgium, France, and South Africa adhered to the most principles whilst Bulgaria, Egypt, Hungary and Romania had the most instances of non-adherence. Most countries adhered to using ex-factory prices, aligning ERP systems with negotiation tools and keeping price revisions to the minimum.

Table 18: Adherence to the 14 best practice principles

	Clear objectives aligning with policy goals	Focus on on-patent drugs	ERP prices do not over-ride HTA decisions	Administra-tively simple and trans-parent	Stake-holder partici-pation	Possi-bility to appeal	Appro-priate country selection	Consider-ation of in-ternational implications	Use of ex-factory prices	Use of mean prices	Respect of patent status	Avoid impact of exchange rate	Price revisions to the minimum	Alignment with negotia-tion tools
Austria	✓	?	?	×	×	✓	✓	✓	✓	✓	?	?	×	✓
Belgium	×	✓	✓	×	×	✓	✓	✓	✓	✓	✓	?	✓	✓
Bulgaria	✓	×	×	×	×	✓	×	✓	✓	×		×	×	✓
Czech Republic	✓	?	×	×	×	✓	?	✓	✓	×	×	×	×	✓
Estonia	✓	?	✓	✓	×	×	?	✓	✓	×	×	×	×	✓
France	✓	✓	✓	✓	×	×	✓	✓	?	×	✓	✓	✓	✓
Germany	N/A	✓	✓	✓	×	N/A	✓	×	×	✓	×	✓	✓	✓
Greece	✓	✓	N/A	×	×	✓	×	✓	✓	×	?	×	×	✓
Hungary	✓	✓	×	×	×	×	×	×	✓	×	✓	×	✓	✓
Italy	?	✓	✓	×	×	×	✓	✓	✓	✓	?	?	✓	✓
Latvia	✓	?	✓	✓	×		?	✓	✓	×	?	?	✓	?
Poland	×	?	?	×	×	×	×	✓	✓	×	?	×	✓	✓
Portugal	?	×	?	✓	×	✓	✓	✓	✓	✓	?	?	×	✓
Romania	×	×	N/A	×	×	×	×	×	✓	×	✓	×	×	✓
Slovakia	✓	?	?	×	×	✓	×	✓	✓	×	×	✓	×	✓
Slovenia	?	?	?	✓	×	✓	?	✓	✓	×	?	?	×	?
Spain	×	?	✓	×	×	✓	×	×	✓	×	✓	✓	✓	✓
Egypt	✓	✓	N/A	×	✓	✓	×	×	×	×	×	×	✓	✓
Jordan	?	?	N/A	×	?	?	?	×	✓	✓	?	×	✓	?
Kuwait	?	?	N/A	✓	?	?	?	×	?	?	?	?	✓	✓
Lebanon	?	×	N/A	×	?	?	×	×	×	×	?	×	✓	?
Qatar	?	?	N/A	✓	?	?	?	×	?	?	?	?	✓	?
Saudi Arabia	?	?	N/A	×	?	?	?	×	✓	×	?	?	?	?
UAE	?	?	N/A		?	?	?	×	×	×	?	?	?	?
Brazil	✓	✓	✓	×	×	✓	×	✓	✓	×	×	×	✓	✓
Russia	✓	✓	N/A	×	✓	×	×	×	×	×	×	×	✓	?
South Korea	?	✓	×	✓	?	?	×	×	✓	✓	?	?	?	?
Turkey	?	✓	×	✓	?	✓	?	×	✓	×	?	✓	×	?
South Africa	✓	✓	N/A	✓	✓	✓	×	×	✓	×	✓	✓	✓	?

Notes: ✓ Country follows principle; × Country does not follow principle; ? Ambiguous, more than likely country does not follow principle

5. CONCLUSION

This paper aimed to identify detailed evidence on the methods by which ERP is implemented in 29 countries using a systematic review process combined with a survey of key informants. Of these 29 countries, 17 were EU member states with the remainder representative of the Middle East, South America and the rest of the world.

A set of 17 criteria (endpoints), divided into two groups – "structural elements" and "interaction with other policies" – were used to collect data on ERP systems with countries benchmarked against these endpoints. Our findings showed that there is significant heterogeneity between countries in terms of the design of their ERP systems. Subsequent analysis highlighted the fact that none of the countries in question adhered to the 14 best practice principles thought to form an 'optimal' ERP system. There are a number of policy implications arising from heterogeneity and suboptimal practices, particularly when countries focus on using lowest price calculations and high-income countries reference lower priced countries with no wealth adjustment. These practices could undermine any potential beneficial ERP effects for government payers such as cost-containment and low pharmaceutical prices. Suboptimal practices can cause spillover effects such as launch delays in low-income countries, inflated prices relative to GDP in some countries, globally declining pharmaceutical prices, reduced incentive for continued R&D and reduced access to medicines in some regions. This is in direct contrast to the aims of ERP.

Rapidly evolving healthcare costs and increases in life expectancy and chronic disease prevalence mean that reduced drug prices are the ultimate aim for most country governments. But, carelessly employed ERP, which could be detrimental to all stakeholders, should be avoided at all costs. ERP systems should be designed with both health and industrial policy aims in mind. Schemes have to represent the requirements of all stakeholders including patients, manufacturers and governments in order to ensure that patients get access to well-priced medicines as and when required, governments can spend within their means and manufacturers have enough incentive to continue investing in future R&D in order to benefit future patient populations. Developing such a system will require input from all actors during the design and review of ERP systems.

Results from this paper, as well as the alternative paper in this series on the impact of different ERP systems, have shown that heterogeneity and suboptimal ERP practices can have detrimental effects for all stakeholders. Overcoming such issues in a non-partisan, systematic way can be achieved using the set of 14 best practice principles discussed here. By following such guidelines, it is hoped that ERP systems that are of benefit to all stakeholders and lead to fair pricing and equitable access to health technologies, whilst improving the sustainability of pharmaceutical pricing practices and encouraging innovation, can be developed.

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APPENDIX 1

Framework of 14 principles for optimal ERP implementation (Sullivan et al. 2017)

Principles	
1	The objectives of ERP systems should be clear and align with health system objectives
2	ERP systems should focus on on-patent products considered for the purposes of coverage, pricing and reimbursement decisions
3	Prices developed via ERP do not over-ride HTA conclusions or VBP approaches
4	The ERP system should have administrative simplicity and transparency
5	Stakeholders should participate in design and review of ERP system
6	Stakeholders are able to appeal regulator decisions
7	Reference countries should be selected based on similarities in economic status and health system objectives
8	International implications of ERP implementation should be considered
9	Publicly available ex-factory prices should form the basis of the ERP system
10	The mean of prices in reference countries should be used
11	ERP system respects patent status of products it covers based on provision of IP that prevail in reference country
12	ERP formula should avoid the impact of exchange rate volatility
13	Price revisions should be kept to a minimum and should be carried out consistently to avoid the perception of opportunistic behaviour
14	ERP-based prices should be aligned with other tools used when negotiating reimbursement