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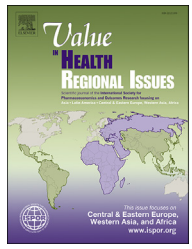

Health Policy Analysis

External Reference Pricing for Pharmaceuticals—A Survey and Literature Review to Describe Best Practices for Countries With Expanding Healthcare Coverage

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ABSTRACT

Background: Countries with expanding healthcare coverage (CEHCs) increasingly use external reference pricing (ERP) for pharmaceuticals. The ERP policies must aim to optimize efficiency, minimize disturbances, and maximize access to effective therapies for all patients. **Objective:** This research aims to deduce best practices for prudent ERP regulations from past experiences and currently applied policies and to guide policymakers in CEHCs in implementing robust ERP policies. **Methods:** The literature was reviewed for methods and effects of ERP for pharmaceuticals. Pharmaceutical pricing experts from Asia, the Middle East, Russia, and South Africa were surveyed for current approaches to ERP in their respective countries. **Results:** Key determinants of ERP relate to scope, number, and choice of reference countries; price definitions; computation rules; frequency; and stringency of applying ERP. The scarce evidence shows that ERP seems to lead to narrower price windows with the risk of reducing prices in high-price countries and raising prices in low-price countries. Moreover, launch delays and indirect price effects are often observed. The ERP policies in CEHCs are often applied in isolation, not always in a consistent and transparent manner, neglecting its indirect effects. **Conclusion:** Policymakers should consider a set of requirements when introducing ERP, including clear definitions and decision criteria in full transparency. External reference pricing should inform and serve as a benchmark for pricing decisions, rather than being used as the sole pricing mechanism. External reference pricing is primarily a tool to support decisions regarding on-patent pharmaceuticals, and for off-patent products, competition may prove more effective in reducing prices than ERP.

Keywords: developing countries, emerging markets, external reference pricing (ERP), good practice, international reference pricing (IRP), pharmaceuticals, pricing policy.

Introduction

External reference pricing (ERP), also known as international reference pricing, international price comparison, external price referencing, or cross-reference pricing, was defined by the World Health Organization (WHO) Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies as a price policy whereby a government compares the price of a medicine to one or several other countries to derive a benchmark or reference price for the purpose of setting or negotiating the price or reimbursement rate of the product in the own country or context.[1] External reference pricing is a price regulation tool used to contain cost and to ensure that the price paid for a pharmaceutical product in a country or payer organization does not exceed unreasonably the price paid in the comparator countries or organizations.[2-4] It may be used formally or informally to set ex-factory and retail prices, at launch or during the product life cycle on a regular basis, or as the primary or as one of several criteria for informing the price setting or revision.[2,5]

Compared with other more rigorous approaches to setting prices, ERP seems relatively intuitive and easy. Moreover, it provides reassurance for the public that prices do not exceed those in other countries. Therefore, ERP is commonly applied for newly

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Table 1 – ERP rules summary table.

		#	Detail
Asia			
Korea, Rep.	KR	8	ERP to determine price caps—not consistent
Pakistan	PK	5	From lowest price to average price (2018)
Philippines	PH	2	ERP possible to similar income countries
Taiwan	TW	10	Median price may define upper price for on-patent drugs
Vietnam	VN	4	ERF to orient CIF price—not defined how
Russia, Ukraine, Kazakhstan			
Kazakhstan	KZ	40	MAH submits prices at any registration change/update; new regulation since 2018
Russian Fed.	RU	20	Essential drug list; MAH submits prices
Ukraine	UA	5	For affordable medicines pilot; price corrections within 5 days, review twice/year
Latin America			
Brazil	BR	9	Formal ERP to lowest private market price; informal use in public market
Colombia	CO	17	ERP used as benchmark for IRP for drug groups
Ecuador	EC	9	Average of 3 lowest prices determines maximum public sales price for strategic new medicines
Mexico	MX	9	Different rules in private and public sector for patented medicines
Middle East, Maghreb, South Africa			
Algeria	DZ	8	Between 0% and 10% below lowest price FOB
Bahrain	BH	31	Mix of ERP and IRP for all drugs
Egypt	EG	36	10% below lowest price; MAH submits ex-factory, CIF, retail price
Iran, Isl. Rep.	IR	3	Lowest international price defines maximum local price; includes Gx
Iraq	IQ	20	Mandatory for all marketed drugs; lowest price (ex-manufacturer)
Jordan	JO	17	Public price of branded products with multilevel comparison
Lebanon	LB	14	Patented and Gx using lowest price: MAH reduce within 10 days if price falls in any reference country
Oman	OM	31	All drugs based on CIF; mix of ERP and IRP
Saudi Arabia	SA	30	On-patent drugs with CIF, ex-factory, and wholesaler price
Turkey	TR	5	Lowest ex-factory price; exchange rate = 70% of average previous year
United Arab Emirates	UE	6	Lowest price in basket for on-patent and Gx drugs
South Africa	ZA	4	MAH submits ex-factory price for on-patent drugs

Note. For each referencing country, the number of reference countries and key referencing rules are summarized. The country abbreviations follow the International Organization for Standardization codes: https://www.iso.org/iso-3166-country-codes.html. The table was adapted from the survey results and complemented and updated with information from HIS Global Insights (August 2018).
# indicates number of reference countries; CIF, cost, insurance, and freight; ERP, external reference price; FOB, free on board; Gx, generics; IRP, internal (national) reference price; MAH, marketing authorization holder.

introduced medicines in all countries of the European Union and the European Free Trade Association except the UK and Sweden, which prefer to apply value-based pricing methods.[6,7] In addition, many low- and middle-income countries have started or are considering adopting ERP policies.[2,4] Often, the ERP policies are considered when progressing in building and expanding the healthcare (HC) systems toward universal health coverage. In addition to improving access to HC, most importantly for the less affluent population, expanding HC coverage has economic consequences owing to increasing HC consumption and an increasing number of products and services to be paid by the HC payer such as national or insurance funds. To minimize the increase in cost and the burden on their budgets, the payers in the countries with expanding healthcare coverage (CEHC) create various mechanisms to ensure that products are acquired at the lowest possible cost.[8,9] Aggravating circumstances are that the supporting infrastructure or legal frameworks in CEHCs may be limited and, in addition, they may affect other countries by becoming exporters of prices. In the long run, ERP may not lead to the desired result of price reduction and expanded access to medicines for the domestic population if the regulatory framework is not shaped to maximize efficiency for payers and access to effective therapies for all patients without creating disturbances of HC.[10]

In this article we propose that the experience with ERP in countries with mature HC coverage systems over the last couple of decades should be adapted and guide CEHCs when introducing ERP as a pricing policy.

Objectives

The purpose of this article is to specify how ERP can be applied best to achieve the goal of maximizing access to effective pharmaceutical products for the population in CEHCs at reasonable cost. For this, we will review the current use and effects of ERP in both countries with mature HC coverage systems and CEHCs based on the published evidence and on a survey among pharmaceutical pricing stakeholders on the current use and state of the art in CEHCs. Best practices for a prudent ERP regulation will be deduced from the reviewed evidence to guide policymakers to apply ERP effectively while mitigating the potential risks of defective ERP policies.

Methods

The scientific and gray literature was screened in a pragmatic approach by using internet search engines (Google, DuckDuckGo); electronic article databases (PubMed, Embase); and websites of relevant organizations such as the WHO, Österreichisches

Bundesinstitut für Gesundheitswesen, Austria, Organisation for Economic Co-operation and Development, and International Society for Pharmacoeconomics and Outcomes Research. The goals were to retrieve information (reports, analyses, meta-analyses) relating to the methods or effects of ERP for pharmaceuticals. The search terms were combinations of at least 2 of the following groups of terms: (1) pharmaceuticals; (2) international or external reference pricing or external price referencing; (3) methods or regulation; and (4) impact, effect, or outcomes. In addition, the references used in key publications were reviewed and included if relevant.

Simultaneously, a survey was conducted among pharmaceutical industry experts to identify currently applied mechanisms and approaches to ERP in 17 CEHCs in the Middle East (Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates), Asia (Kazakhstan, Pakistan), Algeria, the Russian Federation, Ukraine, and South Africa. The questionnaire (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.04.003) was completed between March and July 2017; all responders were employees working as market access professionals in the country affiliates of Abbott (Established Products Division), all trained and experienced in purchasing, pricing, and reimbursement mechanisms of off-patent pharmaceuticals. The selection of the survey target countries was based on the accessibility of appropriate local market access personnel. By sourcing the information from these individuals, it was possible to achieve a 100% response rate with a level of intra-company semantic consistency. The responses were evaluated and summarized by the research team. Nevertheless, because some countries such as those from Latin America were not covered in the survey, the results were complemented by extracting summary referencing information from commercial pricing data services of IHS Global Insights (Life Sciences: International Reference Pricing) to cover a broader range of countries across Asia, the Middle East and Africa, and Latin America (Table 1 and Fig. 1), and to cross-check (validate) the responses given in the survey.

Results

We identified 30 publications for inclusion in the analysis for this review, of which 22 discussed the impact of ERP.[2,4-7,11-35] Most research relating to ERP methodologies and effects has been conducted in countries with mature HC coverage systems, where the first ERP systems were introduced many years ago (ie, mostly in Europe). Among these, a few systematic analyses and reports have been performed throughout the last decade.[2,4,7,14,19,20] Although there is general agreement that ERP offers a good opportunity to benchmark the price of medicines against similar regions and to avoid excess prices in the own country, many authors have expressed concerns relating to the potential negative consequences of ERP[2,4,6,7,11-13,18,25-31,33,34] or its limited effect.[17] In the following sections, we will first summarize ERP application in mature HC coverage systems and in CEHCs (based on our survey) and subsequently derive the impacts of ERP as observed or discussed around the world. Because few publications relate to ERP in CEHCs,[2,4,13] we sought more information through our survey.

ERP in Europe and Other Countries With Mature HC Coverage Systems

In Europe, pharmaceutical ERP is omnipresent but heterogenous.[14] According to an ERP mapping performed in 2014 and a survey conducted in 2015, 9 European countries (Belgium, Finland, France, Germany, Italy, Latvia, Poland, Slovenia, and Spain) used ERP as a supportive criterion to determine the domestic price or reimbursement of new pharmaceuticals; another 20 countries applied ERP as the main or sole systematic criterion when setting prices of new drugs; and the UK and Sweden used only other means to determine the price.[2,4,15] Other important criteria considered in price-setting include (1) the cost of therapy cycle, (2) health gain from the patient perspective, (3) cost-effectiveness, (4) relative benefits compared with treatment alternatives, (5) budget impact analysis, (6) financial resources available for reimbursement, and (7) reward for innovation.[2,5]

Frameworks for ERP in mature HC coverage systems (see Table 2) display high diversity. Most countries apply ERP for on-patent pharmaceuticals only, with variations in the scope. The composition of price baskets and the computation of prices are highly variable, as are the frequency of the exercise and other important characteristics. Since ERP was first applied in Europe, changes have been introduced to update the ERP regulations, often triggered by difficult economic situations such as the financial crisis or political decisions relating to the pharmaceutical budget.[5] The European Integrated Price Information Database collaboration intends to develop a technical guidance document on a coordinated approach regarding external reference pricing with the intention of avoiding or mitigating potential negative impact for patient access to medicines because of imprudent use of ERP policies.[36]

Beyond Europe, ERP is being used in other countries with mature HC coverage systems, such as Australia, Canada, Israel, Japan, and New Zealand. Except Israel, where ERP is applied to pharmaceuticals in general, all other countries use it for on-patent products only. Some, like Australia,[7,16] consider ERP as one of several criteria supporting pricing negotiations or in informal ways such as used by New Zealand.[7] Like in Europe, no common approaches are observed and great variation exists in the scope, use, and application.[2,5] Publications with high-level scientific evidence on the impact of ERP are scarce and derive different conclusions depending on the researcher's perspective.[5]

Features of ERP Systems in CEHCs

A tabulated overview of the ERP processes resulting from this study's survey can be viewed in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.04.003. No common practice was recognized across the countries and, as summarized in Table 2, there are significant differences in the scope, composition of baskets, computation of prices, and frequency of revisions. Table 1 expands on the survey results by adding information on key ERP rules applied in additional countries in other regions (Latin America and Asia) and confirms the observations obtained from the survey.

Figure 1 summarizes the cross-country referencing dependencies and country baskets in CEHCs. Again, size and composition of country basket varied widely. Some countries of the Middle East, Russia, and Kazakhstan review a very high number of reference countries (20-40 countries). Asian and Latin American countries have defined much smaller reference baskets.[5-17]

Differences in ERP Application in Countries With Mature HC Coverage Systems and CEHCs

When comparing the use of ERP in countries with mature HC coverage systems, such as the Western European countries, Canada, or Australia, with the CEHCs in our survey, a few important differences can be observed.

Scope of products

In most countries with mature HC coverage systems, ERP is only applied to innovative on-patent products. In contrast, CEHCs tend

Asia

	AU	BE	KH	CA	FR	DE	IN	ID	IT	JP	LA	LB	MY	PH	LK	SE	CH	TW	TH	GB	US	#
KR					X	X			X	X							X	(x)		X	X	8
PK								X				X	X	X	X							5
PH							(x)												(x)			2
TW	X	X		X	X	X				X						X	X			X	X	10
VN			(x)								(x)		(x)						(x)			4

Russia, Ukraine, Kazakhstan

	AM	AU	AT	BY	BE	BG	CA	CL	HR	CZ	DK	EE	FI	FR	DE	GR	HU	IS	IE	IL	IT	JP	KZ	KR	KG	LV	LU	MX	NL	NZ	NO	PL	PT	RO	RU	SK	SI	ES	SE	CH	TR	UA	GB	US	COO	Count
KZ	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	(x)	X	X		40
RU				X	X	X			X	X	X			X		X	X		X		X		X						X		X	X	X		X		X			X	X			X	20
UA										X							X										X					X													5

Latin America

	AR	AU	BR	CA	CL	CO	EC	FR	DE	GR	IT	KR	MX	NZ	NO	PA	PY	PE	PT	ES	TR	GB	US	UY	COO	Count
BR		X		X				X			X	X		X					X	X			X		X	9
CO	X	X	X	X	X		X	X	X				X		X	X		X	X	X		X	X	X		17
EC			X	X	X	X							X				X	X					X	X		9
MX	X		X	X	X	X		X				X									X		X			9

MiddleEast, Maghreb, South Africa

	DZ	AR	AU	AT	BH	BE	CA	HR	CY	CZ	DK	EG	FI	FR	DE	GR	HU	IN	IR	IE	IT	JP	JO	KR	KW	LB	MA	NL	NZ	NO	OM	PH	PL	PT	QA	SA	ES	SD	SE	CH	TN	TR	UE	GB	YE	COO	Count
DZ						X								X		X											X										X					X	X		X		X	8
BH	X	X	X			X	X		X		X	X		X	X	X	X			X	X	X	X	X	X	X		X	X		X			X	X	X	X		X	X		X	X	X			31
EG	X	X		X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X		X	X	X	X		X	X		X	X	X			36
IR																X																					X							X				3
IQ				X	X	X	X			X				X	X				X				X		X			X	X		X			X		X	X			X			X	X	X			20
JO				X	X		X		X	X	X			X		X	X				X	X						X	X					X		X	X							X				17
LB						X	X							X							X		X		X						X			X	X	X	X			X				X	X			14
OM	X	X	X			X	X	X		X	X			X	X	X	X			X	X	X	X	X	X	X		X	X					X	X	X	X			X	X		X	X	X		X	31
SA	X	X	X			X	X	X		X	X			X	X	X	X			X	X	X	X	X	X	X		X	X		X			X		X	X			X	X		X	X	X			30
TR														X		X					X													X			X											5
UE						X																			X						X				X	X									X	X		6
ZA			X				X																					X									X												4

Fig. 1 – ERP referencing matrix tables. The referencing countries are in the rows and the reference countries in the columns. The numbers (#) are the number of reference countries for the country in this row. The country abbreviations follow the International Organization for Standardization codes: https://www.iso.org/iso-3166-country-codes.html. The tables were adapted from the survey results and complemented and updated with information from HIS Global Insights (August 2018). ERP indicates external reference price.

to apply ERP much more broadly, including the use for off-patent products and for non-reimbursed products.

Stage in the life cycle of the product

Usually, innovative pharmaceuticals are launched in countries with mature HC coverage systems within a short time window. At the time of launch in CEHCs, however, the product may already be on the market for many years in other countries. Hence, the stage of the life cycle, the target patient population, and the value framework may not be comparable, and direct price comparison may distort the value picture.

Source of price information

Most CEHCs rely on information from the manufacturer or distributor for the price comparison. Manufacturers have a good overview on prices of their own products; however, the competitors' (net) prices are only known if they were published. In European countries, multiple official sources are consulted to consolidate credible comparative price information. Such sources rarely exist in CEHCs.

Definition of price

There is a tremendous variability in which price components are included in the comparison. The less well defined these cost components are (eg, including or excluding transportation and distribution cost, consideration of import taxes), the less robust is the comparison.

Impact of ERP

External reference pricing, in principle, is described as one piece of information, complemented by others, for deriving appropriate prices for new pharmaceuticals.[7] Several authors concluded that ERP will effect some reduction in prices.[18,19,21,22] On the other hand, evidence is scarce on the concrete direct or indirect impact of ERP on prices, access, availability, quality, and HC in the long run.[5] In Table 3, the impact on price levels and patient access is summarized. External reference pricing has been described as an inefficient approach to reducing prices when used in isolation from other pricing policies, and therefore more value is seen in combinations of price policies.[7] Where ERP is used to define price ceilings, this may inhibit further reduction of prices below the ceiling even if there is competition.[23,32] The inefficiency of ERP as a primary pricing mechanism is confirmed by the large variation in price levels among countries using ERP.[19,20] This is not surprising when considering the high variability in the application of ERP across different settings and the creative variation in terminology, semantics, and practices.[24]

Reports agree that manufacturers will respond to ERP with a range of strategies to minimize the impact on the business, including strategic launch sequencing to minimize price erosion and generally closer management of launch prices within narrow price windows to minimize the cross-country influence.[12,25-27] In consequence, those countries willing to pay higher prices will be preferred for early launches while those with lower ability or willingness to pay tend to see launch delays until the product is introduced and priced in the (wealthier) high-price

Table 2 – Summary of pharmaceutical ERP frameworks in countries with mature HC coverage systems[2,4,7,15,20] and CEHCs (resulting from survey with 17 CEHCs).

ERP aspect	Countries with mature HC coverage systems	CEHCs
Scope of ERP	Almost all countries use ERP for on-patent prescription medicines, although with large differences in the extent (eg, originator medicines, on-patent, only for hospital use, only reimbursed on-patent medicines). Only a few countries apply ERP for generics (Austria, Croatia, Czech Republic, Latvia, Lithuania, Luxemburg, Netherlands).	ERP is used formally or informally in connection with mandatory price registration for all marketed pharmaceutical products in some form in 15 of the 17 surveyed countries. The exceptions are Russia and Kazakhstan, where it is only applied for the products on the essential drug list or for the reimbursed products, respectively.
Composition and size of country basket	The reference countries are often chosen for geographic proximity or for economic similarity. There is a great variation in the number of countries included in the reference country basket, ranging from 1 for Luxemburg (using country of origin) to 30 for Poland and Hungary.	There is a large variability in which and how many countries are used in the reference basket, ranging from 4 in Iran to 36 in Egypt. Qatar and UE are referencing only to the country of origin, though it was not defined whether the country of origin refers to the country that manufactures the drug or the marketing authorization holder country.
Price calculation and reference units	The computation methods are not always clearly defined and can vary from one type of product to another (brand versus generic; outpatient vs inpatient) within the same country. Most commonly, the average price of reference countries is calculated (Austria, Belgium, Cyprus, Ireland, Portugal, Switzerland, and The Netherlands). Others use the lowest price (Bulgaria, Hungary, Italy, Romania, and Spain) or the average of the 3 or 4 lowest prices (Czech Republic, Greece, Norway, and Slovakia), some countries specifically refer to the second, third, or fourth lowest price or use a combination of limitation rules (eg, not higher than the highest, not cheaper than the lowest) or include calculations to ensure lower prices (eg, $\times$ -10%) or ensure extra margin to acknowledge the investment in research and innovation (eg, $\times$ + 10%). There is no agreement on the most appropriate pharmaceutical presentation (ie, defined by pharmaceutical form, pack size, and strength). Some use the closest pack size, others a percentage band around the local pack size, the same dosage (price/unit or price/DDD), the therapy cost, and some only allow reference to exactly the same product and presentation.	Most frequently, the lowest price from the reference countries in the basket will be the decision base. If the European price is the lowest, Algeria will request a mandatory reduction by 10%. For Egypt and Kazakhstan, there is no explicit rule for the lowest price.
Source of price information	The prices are usually summarized by the marketing authorization holder as list prices or real prices. Some countries' competent authorities perform an additional independent price search (eg, from official websites and databases such as the Austrian Public Health Institute's Pharma Price Information service, or through a network such as the EURIPID database).	Most countries source the prices from publicly accessible information, from the market authorization holder (eg, Algeria, South Africa), from price certificates (eg, Iran, Iraq), or from tender prices (eg, Iraq). Some countries have price disclosure agreements with other regions (European countries, Australia, UK) or request the prices from other sources (eg, IMS/IQVIA, the country's representation in the basket country, or charted accountants).
Definition of price	Most countries reference the ex-factory price (manufacturer price); other uses the pharmacy purchasing price or the pharmacy retail price.	The most frequent price sought in the reference countries is the wholesaler purchasing price (Bahrain, Iran, Iraq, Jordan, Kazakhstan, Lebanon, South Africa, and Ukraine), followed by the public price, which included VAT in Algeria and Bahrain and excluded VAT in Pakistan. Russia allows for adding cost of customs duties, and some rules (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and UE) refer to the lowest cost, insurance, and freight or the free-on-board price in the country of origin and of those of 30 other countries, where the product is marketed at the time of price submission.

continued on next page

Table 2 – *continued*

ERP aspect	Countries with mature HC coverage systems	CEHCs
Frequency of price revisions	Price revision can be initiated by major changes or rule based (eg, for the products with the highest turnover in Norway), or in a regular (every 6 months, yearly, 2-year, etc.) or irregular frequency.	Prices can be revised yearly (Algeria, Kazakhstan, and in the future Pakistan), every 2 years (South Africa), every 5 years (Lebanon), on an irregular basis (Egypt), only at launch or inclusion (Ukraine, Iran, Russia), or ad hoc with changes in the reference countries or the product properties (Algeria, Lebanon, Jordan).
Calculation if the price is missing for reference countries	Various methods or algorithms are used by different countries when not all prices in all reference countries are available.	Usually not defined

CEHC indicates countries with expanding healthcare coverage; DDD, defined daily dose; ERP, external reference pricing; EURIPID, European Integrated Price Information Database; HC, healthcare; VAT, value-added tax; UE, United Arab Emirates.

countries.[6,7,15,25-30] In general, product availability may be more compromised in countries with lower prices and higher chances for parallel export.[19] This also implies a higher risk for drug shortages for these countries.[15,28] On the other hand, countries with large market volumes seem to remain unaffected by cross-dependencies (even if they are referenced by many other countries).[29]

Moreover, to avoid launch delays, countries with small market volumes, especially those with lower income and price levels, may have to accept higher price levels than they would have been able to negotiate with the manufacturers if they were not referenced by any other country, which will result in several years of excessive expenditure.[6,29] Studies comparing prices[13] or modeling the impact of cost containment policies including ERP across European countries[11,31] have confirmed the relatively higher prices and expenditures in lower-income countries with ERP, whereas the larger and more affluent countries can achieve major savings through ERP.[31]

The pharmaceutical price convergence among European countries before the economic crisis in 2008 provided a reasonable explanation of the higher growth rate of pharmaceutical expenditure in lower-income countries, which ultimately resulted in disproportionately more cost-containment measures in lower-income countries compared to higher-income countries after 2008.[11]

Furthermore, if prices fall in one of the countries in the network due to events unrelated to the value of the pharmaceutical products (eg, price cut due to economic crisis, indirect cut through inflation or through an exchange rate drop), sooner or later all the countries in the referencing network may follow despite not sharing the same economic conditions.[32]

It has been criticized that countries that rely on ERP basically borrow the work of value assessment performed in other countries (assuming that it has been done) with different value frameworks.[33] With many countries using ERP, a race to-the-bottom tendency was observed, as every country attempted to get a better deal than other similarly situated countries.[34]

Therefore, it was advised to restrict the comparison to smaller groups of countries with a similar economic situation and HC frameworks.[35]

Table 3 – Summary of impact of ERP on price levels and access as reported in the literature.

ERP aspect	Impact on price level	Impact on access
ERP as benchmark for innovative drugs in combination with other pricing methods	Avoid excess prices[7,18,19,21,22]	Evidence not conclusive[5]
ERP as only method for pricing of innovative medicines	Reduces prices inefficiently[7]	Evidence not conclusive[5]
ERP is used to define price ceilings	Prices drop to ceiling but not below[23,32]	
ERP rules across countries with variability in the layout	Strategic launch planning of companies to keep prices in narrow price window for a long time[12,25-27] Race-to-the-bottom effect[34]	Reduced access in countries with delayed launch due to unfavorable ERP rules[6,7,15,19,25-30]
Being in country basket for countries with higher price level	Price level only within the price window defined by company; prices higher than without ERP[6,11,13,29,31]	Higher risk for drug shortages in low-price countries[15,19,28]
ERP in high-price countries	Reduction of price levels in high-income countries[31]	
Impact of price cut mandate in one of the basket countries	Domino effect on other countries; price reduction but without policy mandate[32]	Higher risk for drug shortages in lowest-price countries[32] or in country with price cut mandate

ERP indicates external reference price.

Table 4 – Summary of challenges related to the key aspects of ERP regulations.

ERP aspect	Challenges
Scope of ERP	ERP can support benchmarking in a monopolistic situation. Nevertheless, when applied where competition exists, it may inhibit the competitive forces.
Composition of country basket	ERP is easier than a complete value analysis for new pharmaceuticals, but the price should reflect the HC-specific value of a product. The comparison to prices that other countries pay implies that those reference countries operate in the same value framework.[6,33] Referencing to other HC frameworks distorts the price-value relationship. The complexity, administrative burden, and risk of interference by factors not related to the product increase with the number of reference countries.
Definition of price	There is a lack of definition (ex-manufacturer price, wholesaler price, tax or customs included or not, etc.) and a considerable variability of prices (eg, rebates, clawbacks, price volume contracts). With increasing personalized medicine, risk-sharing, or similar agreements, a fixed price may no longer exist.[6]
Source of price information	Unbiased public price information is not available. Final prices (net prices) often are not disclosed; the manufacturer has only limited incentive in sharing the contract details and they do not know the competitors' net prices. An attempt to create price transparency in Europe by collecting all price information (including prices resulting from tenders or rebates) in a central database[15] is the database EURIPID.* This database is not public and not accessible for manufacturers, and the content cannot be validated. Special contractual agreements may not be shared, because such communication would likely end such agreements.
Price calculation and reference units	Different presentations (formulations, sizes) of medicines impede comparison even among products from the same manufacturer. Yet more complex are comparisons across several products from different manufacturers. The resulting price is often determined by a formula (eg, lowest, average, average of 3 lowest). Many countries with tight HC budgets aim to pay the lowest price; some even request the lowest minus a certain percentage. This behavior will drive all the prices in the reference network down—the so-called race-to-the-bottom effect—and put the sustainability at risk.[34] Sudden changes in national policies, changes in exchange rates, or different levels of inflation cause additional uncertainty unrelated to the product value.
PPP adjustment of exchange rate	If higher income countries reference lower income countries by using actual exchange rates without adjustment to differences in purchasing power, the price convergence may result in a higher growth rate of pharmaceutical expenditure in lower income countries, which ultimately necessitates disproportionately more cost-containment measures in lower-income compared to higher-income countries.
Frequency of price revisions	A high frequency of price revisions with short run-in times can lead to fast price erosion. A serious tradeoff with frequent price revisions is that the entire supply chain will only keep minimum stock to avoid frequent stock devaluations. This increases the risk of medicine shortage, especially for the 2-3 months before a scheduled price revision.

ERP indicates external reference price; PPP, purchasing power parity.
* European Integrated Price Information Database (www.euripid.eu).

Discussion

External reference pricing was first broadly introduced in Europe, where with the centralized market authorization procedure most drugs become available within a relatively short time frame during an early phase of their overall life cycle.[6] The introduction of a uniform currency in some of the European countries facilitated the comparison. Nevertheless, what seems intuitively right comes along with some challenges.

External reference pricing is usually created in isolation country by country, often not considering the interlinkage and interdependency. Although it is desirable that countries strive to introduce pharmaceutical policies and, more specifically, pricing polies that support the national HC priorities, a better coordination and cross-country learning could lead to higher efficiency by avoiding or reducing potential risks. An example for such collaborations and cross-country learning initiatives in Europe would be the European Integrated Price Information Database project supported by the European Union commission.[36]

Challenges of ERP

As shown in our review, a plethora of different methods and definitions is applied across the world with a large degree of interdependencies and risks for immediate and long-term chain reactions across countries. These chain reactions can be initiated by events that are not at all related to HC, such as the economic crisis in Greece and the subsequent economic austerity measures in 2010 and after. The potential pitfalls of ERP are located on both the macroeconomic level (composition of prices across countries, differences of wealth and willingness to pay among countries, exchange rate fluctuations) and the microeconomic level (differences in the HC structure and objectives, differences in medicine formulations, pack sizes or stage in life cycle, differences in epidemiology and indication). Specific risks that are potentially associated with the key pillars of ERP regulations are summarized in Table 4. The race-to-the bottom price effect and economic uncertainty can impede the availability of products in the market on one hand and, on the other hand, investment in new products by pharmaceutical companies will decline in low-price countries.[6] Hence, public health and economy ultimately may suffer.[13]

Stakeholders in ERP

The key stakeholders concerned by ERP include (1) patients; (2) competent authorities for pharmaceutical pricing, reimbursement, and health technology assessment; (3) public and private

Table 5 – Recommendations for the use of ERP as a national pricing policy.

ERP aspect	Recommendation	Rationale
Directly related to ERP		
Scope of ERP	Reimbursement of single-source products (on-patent pharmaceuticals).	Off-patent and generic medications are subject to greater competitive forces, which drive price erosion; competition is more effective than regulation in this segment; there are also other mechanisms available for regulating prices, such as price capping or internal price referencing.
Composition of country basket	Select 5-7 countries with similar socioeconomic and HC environment.	Keep the administrative burden and complexity low (collection, confirmation, and analysis of information) and have comparable benchmarks.
Definition of price	Ex-factory prices free of markups, taxes, and discounts or rebates should be used. If only other prices are available, establish a transparent and fair conversion algorithm.	The ex-factory price is the most direct reflection of cost of goods and margin, and it is the only criterion that is under the influence of the manufacturer and thus directly comparable between different countries.
Contingency	Stay flexible to adjust for contingencies or temporary distortions (eg, currency devaluation, inflation, other crisis situations).	Protect the system against defects that are not related to the value of the medicines or to the destination country.
Source of price information	Combine official national and international sources and company certified information; critically review and ask for clarification.	If prices are compared, it must be ensured that they reflect the same concept and are composed in the same way.
Price calculation	Calculate the average or median price of the same product (package size, DDD, formulation) in the basket (median if data are skewed).	The price can only be compared if the products are identical; mean or median values are more stable and less sensitive to outliers.
Exchange rate	Prevent volatility by applying s moving average of exchange rates, or average exchange rate for a longer period. Consider using PPP exchange rates, especially if countries with different economic status are in the ERP basket.	Applying daily actual exchange rate may drive opportunistic behavior to revise drug prices on an ad hoc basis and may cause distortions.
Frequency of price revisions	Not more than yearly or biannual and allow reasonable time for implementation.	Allow for business planning and sustainable stock management (pharmacies, wholesalers; industry).
General recommendations for pricing policies		
Incomplete data	Determine temporary prices based on best available evidence (value assessment).	Avoid intuitive decisions or other distortions due to gaps in the information.
Enforcement	Establish clear rules for appeal or for ensuring access in cases of price-related shortages.	Access for patients to their therapies must have priority.
Monitoring	Monitor and evaluate the effects of your pharmaceutical price policies (including ERP). Correct depending on the effects on prices, drug availability, patient access, and investment.	Policies and regulations should achieve the objective for which they were introduced. Correction is necessary if the objectives are not sufficiently achieved.
Complementarity	ERP should be part of a comprehensive pharmaceutical policy.	A country can achieve its HC priorities more efficiently if direct and indirect mechanisms are considered comprehensively for pricing, reimbursement, and consumption of pharmaceuticals.

DDD indicates defined daily dose; ERP, external reference pricing; HC, healthcare; PPP, purchasing power parity.

payers; (4) the generic medicines industry; (5) the research-based pharmaceutical industry; (6) doctors and healthcare providers; (7) pharmacists; and (8) caregivers (persons supporting the patients or in charge of caring for the patients). Each of these stakeholders may have different interests and therefore different preferences when making decisions on therapies or when considering pharmaceutical policies.

A recent survey among stakeholders in Europe on the policy objectives and pharmaceutical pricing and reimbursement, conducted by the WHO Collaborating Centre for Pharmaceutical

Pricing and Reimbursement Policies (Austria), revealed that equitable access to medicines was the highest priority for all stakeholders.[37] Although different value-based methodologies were deemed most appropriate to determine the price, low preference was given to ERP by all groups.

Is ERP an Effective Method for Price Reduction for Off-Patent Products?

Although ERP seems to be easy and intuitive, it is not based on rational economic theory or evidence.[2] Quite the contrary, according to the evidence summarized above, rigid application of ERP in fixing pharmaceutical prices appears to introduce new risks that may antagonize the intended effects. Alternatively, pharmaceutical pricing models that fit prices to income and affordability, such as differential pricing, may lead to fairer prices for single-source pharmaceuticals.[34,35]

Economists and public health researchers around the world suggest that competition is the most effective component in reducing prices and total HC cost, especially in the off-patent space, which concerns most of the drugs in CEHCs.[26,38-41] In the off-patent sector, competitive and dynamic pricing within a framework of integrated cost-containment policies addressing supply and demand will enable products to demonstrate value in the national context and allow access for patients to affordable medicines. Independence from prices in other countries may also motivate manufacturers to consider pricing schemes that are more adapted to the local economic and HC context.[34,42]

Nevertheless, competition only works efficiently where the legal frameworks support the optimal functioning of the market. With the intent of improving access and affordability, many countries regulate prices. To maximize the effectiveness of price policies, promoting a maximum level of competition and avoiding the dissociation of price and quality should remain the primary goals.[43,44]

If there is a rule for ERP at all, it would be that there is no uniform rule. Variations and methodological adaptation to the local context are important to allow alignment with national HC priorities, which most likely differ between countries. Nevertheless, the design of ERP in a country should respect the learnings from international examples of ERP. Public health experts and economists warn that a move toward uniform prices across countries might provoke even more inequity and unfairness and should be avoided as long as there are differences observed in the economies, employment, HC systems, epidemiology, affordability, preferences, or other critical features supporting a higher degree of price differentiation.[34,41]

Recommendations for Best Practices for ERP

Overall, a trend seems to be emerging to use ERP as 1 criterion to be complemented with other direct and indirect pricing policies to form a comprehensive framework supporting the efficient expansion of healthcare coverage. Especially for countries with less resources for a full value analysis, ERP may be a practical and fast approach if a few minimum requirements are met when introducing rules and regulations for ERP in CEHCs. These are summarized in Table 5 for the core pillars of ERP together with a rationale for each of them. The overriding principle should be to use ERP as a benchmark for pricing decisions for on-patent products (scope). The overall HC objectives (eg, better access, cost containment, improved quality) should guide the ERP process. Definitions and decision criteria should be clear and transparent, so that all stakeholders can understand and plan for it. ERP should be embedded in a set of policies, which all drive HC consumption in alignment to the overall HC objectives. And finally, where ERP policies are introduced, the consequences should be recorded and published so that national and international policy researchers and policymakers can learn from them.

Thus, we recommend introducing simple, transparent processes for ERP with a low administrative burden, such as a small country basket of relevant comparator countries or the consistent use of the price elements under direct influence of the manufacturer (ex-manufacturer price). A rational use would include a certain degree of flexibility and contingency processes to remain independent of other countries' economic situation or external value distortions. These include sensible and transparent rules for exchange rate calculation or ERP frequency. To maximize transparency and fairness, the regulation should also specify technical details, such as the compensation for incomplete data or the procedures for enforcement. As with any policy, the impact of ERP should be monitored, and based on these data, the regulation reevaluated regularly (eg, 3-5 years).

Limitations

This research is based on a literature review and a survey among pharmaceutical pricing experts from 17 CEHCs. The literature on the impact of ERP is scarce, because governments tend to not measure the impact of their pricing policies on the HC system in the long term or on results beyond expenditure. Many impact analyses in relation to pricing policies with few exceptions refer only to short-term impact on prices. The results of the survey are limited to the 17 countries and may not be generalizable to other CEHCs or low- and middle-income countries. In addition, the survey reflects the experience of the industry stakeholders.

Conclusion

In this review, we have summarized the current ERP regulations and effects in countries with mature HC coverage systems and in countries in the process of expanding HC coverage as reported in the literature and by surveying industry stakeholders in 17 CEHCs. In addition, we have considered the perspectives and needs of different stakeholders in HC. We conclude that ERP may be used for benchmarking if carefully applied and embedded in well-tuned other policies, all aiming at facilitating the local healthcare system objectives and priorities. Finally, based on the findings in the literature, we deduce guidance for a prudent ERP practice for those CEHCs using or currently introducing ERP policies.

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Supplemental Material

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