



Gesundheit Österreich
Forschungs- und Planungs GmbH



EURIPID

BEST PRACTICE REPORT

on External Reference Pricing (ERP)

23 February 2017, Version 2.0

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European Commission Grant "Statistical data for medicinal product pricing"
under the call HP-PJ-2014 (No. 664317)

Funded by the Health Programme of the European Union

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Forschungs- und Planungs GmbH
February - 2017

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List of abbreviations

ATC	Anatomical Therapeutic Chemical
DDD	Daily defined dose
EC	European Commission
ECB	European Central Bank
ERP	External Reference Pricing
EU	European Union
EURIPID	European Price Information Database
FYROM	Former Yugoslavian Republic of Macedonia
GDP	Gross Domestic Product
GÖG	Gesundheit Österreich GmbH / Austrian Public Health Institute (Austria)
JAZMP	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke / Agency for Medicinal Products and Medical Devices (Slovenia)
HTA	Health Technology Assessment
HIV	Human immunodeficiency virus
IPR	Internal Price Referencing
MAH	Marketing Authorisation Holder
MEA	Managed Entry Agreements
OECD	Organization of economic co-operation and development
OEP	Országos Egészségbiztosítási Pénztár / National Health Insurance Fund (Hungary)
PPP	Purchasing power parities
R&D	Research and development
RPS	Reference Price Systems
SÚKL	Státní ústav pro kontrolu léčiv / State Institute for Drug Control (Czech Republic)
UK	United Kingdom
WHO	World Health Organization

Introduction

This report is a deliverable of the European Commission Grant "Statistical data for medicinal product pricing" under the call HP-PJ-2014 (No. 664317). The grant was awarded to a consortium of five institutions from Austria, Czech Republic (2), Hungary and Sweden. Four of the beneficiaries are members of the Executive Committee of the EURIPID Collaboration.

The overall objective of the grant is not to promote the implementation of External Reference Pricing (further ERP) but to "*achieve a better coordination at the EU level in order to facilitate the control by the Member States of public budgets for medicinal products whilst avoiding/mitigating possible negative impacts on patient access to medicinal care*".

This deliverable refers to the specific objective 3 of the Grant Agreement ("*Developing a guidance document on a coordinated approach of national authorities regarding the use of external reference pricing to avoid/mitigate negative impact for patient access to medicines*"). One task in the frame of the grant is to conduct, amongst others, by the means of literature analysis¹, a review about ERP with special focus on its impacts on patient's access to medicines. The presented results will mainly provide input to work package 6, i.e. the development of a Guidance Document but will also have impact on the further data-set and layout optimization of the database and website (work package 4).

One task is to analyse current practices of ERP in European Countries and derive principles for best practice. In addition, the results will be used as input to one of the main deliverables within the grant agreement, the development of a technical guidance document for ERP.

Purpose of this report

External Price Referencing (ERP) or External Reference Pricing (ERP)² is defined as the practice of "using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country." [1]. In the literature also the terms price cap regulation [2–4], cross-reference pricing [5], geographic price referencing [6] or international reference pricing [7] are used to describe a policy to determine prices of pharmaceuticals based on medicine prices in other countries.

It is important to distinguish ERP from "internal price referencing" (IPR) which is defined as the practice of using the price(s) of identical medicines (ATC 5 level) or similar products (ATC 4 level) or even with therapeutically equivalent treatment (not necessarily a medicine) in a

¹ See Report on the methodology and search strategy "Literature Review 2016–State of Play" provided on 5/7/2016

² The term ERP emphasise the purpose of the policy (i.e. "pricing"), whereas EPR underlines the procedure how prices are derived (i.e. "referencing"). Both terms can be used interchangeably but for the sake of simplicity we will refer consistently to ERP in the report.

country in order to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement of the product in a given country. ERP should also be distinguished from “reference pricing” or “reference price system” (RPS) where the third party payer determines a maximum price (= reference price) to be reimbursed for certain medicines [1].

In the literature, there is often a lack of clear distinction between ERP, IPR and RPS. In contrast to IPR and RPS, ERP is considered to be mainly a tool of pharmaceutical pricing policy. The confusion may be due to the practice of pharmaceutical policy as some countries tend to incorporate elements of ERP in their reimbursements systems [8, 9] and as in some countries pricing and reimbursement procedures are intertwined, having a committee that makes the decisions on both [10, 11].

The rationale of ERP is to contain the costs of medicines under intellectual property rights which enjoy a monopolistic situation [12]. Pharmaceutical markets are imperfect markets suffering from asymmetric information [13] and low price elasticity due to universal health coverage and third party payer [14]. If left unregulated they are prone to market failure (e.g. non-provision of certain goods like orphan medicines) and/or higher prices for medicines [15]. The application of ERP on pharmaceuticals started in the early 90’s, when most industrialised countries faced rising medicines prices while the available health budgets remained nearly unchanged. The next decades witnessed the widespread adoption of ERP among pricing authorities [16]. In 2015, it was the most commonly applied pricing policy in European countries: medicine prices in other countries are considered, at least as a supportive information, in pricing decisions for at least on-patent medicines in the out-patient sector in all EU Member States except Denmark, Sweden and United Kingdom, as well as in some other European countries such as Albania, Iceland, Norway, Switzerland, Former Yugoslavian Republic of Macedonia (FYRM), Serbia and Turkey [17].

The methods for choosing or calculating the external reference price can vary in several aspects (e.g. size of country basket, price types, presentations considered, average vs. lowest price, etc.). However, several methodological problems can occur when prices from other countries are used for the purpose of ERP. The aim of this report is to evaluate current practices of ERP and to develop best practice principles when applying ERP.

The report will not debate the appropriateness of ERP and will not discuss alternative policy options or approaches, but will try to give guidance on how to apply it by avoiding or mitigating potential negative effects on access to medicines by patients.

Methods

This activity is based on the following methodological approaches:

- » **Literature review:** Relevant peer-reviewed articles reviewed with a focus on three aspects: (1) reported effects of ERP e.g. potential harm to patients' access to medicines due to non-availability or in-affordability, (2) impact on controlling national budgets for medicines and (3) on basic "success" factors of this policy.
- » **Grey literature:** In addition to different international databases that have been used to identify articles also grey literature has been searched. Starting point was recommended literature by European Commission, WHO and OECD accompanied with an iterative search of the published and grey literature using Google Scholar and snowballing from forward and back-ward citation searching in key documents
- » **Survey:** GÖG conducted a survey with national and EU authorities, stakeholders in the field of medicines as well as participants of the EURIPID collaboration and asked about their experiences with ERP in the first half of 2016 (for results please see Schneider P, Habl C and Šebesta R [18]). The questionnaire contained 30 questions and was structured in 5 overall topics including open or multiple-choice questions.
- » **Interviews:** Interviews with national pricing and reimbursement experts were conducted as follow-up to the survey by GÖG and OEP. The interviews were semi-structured in order to explore specific questions related to country specific design of ERP methodology.

Principles for best practices

We aimed to identify the problems associated with the policy of ERP from a literature review of peer-reviewed published articles since 2000, grey literature on pharmaceutical pricing and reimbursement, results from a survey and interviews with pricing and reimbursement experts. Based on the results extracted from those sources we developed principles of best practice when applying ERP. We decided to distinguish the principles into three overarching principles each with further explanatory sub-principles.

The first key principle relates to the (A) **regulatory framework in which ERP is embedded**, the second one is dedicated to (B) the **design/structure of an ERP system** and the third one deals (C) with **technical aspects of price comparisons with reference products**.

Especially Principle (C) shall be implemented in the Euripid database in the long run.

Overarching principle A: The objective of the pharmaceutical pricing system should be clear and harmonised with health system objectives and reviewed periodically

Principle #1 Define the objectives of pharmaceutical pricing policy	
<p>The core objectives what national pharmaceutical pricing policy aims at achieving need to be clearly defined in advance. Usual objectives reflect the different dimension of health care systems</p> <ul style="list-style-type: none"> • Cost containment of public funds to ensure long-term sustainability of health care budgets (“public payer perspective”) • Guarantee availability and accessibility of affordable medicines to patients (“patient perspective”) • Demand of revenue stability and reward for innovation for pharmaceutical manufacturers (“producer perspective”)³ <p>Prioritisation of one or more objectives shall be in harmony with the overall objectives of the healthcare system. The objectives of pricing policies, as well as its principles and applied methodologies shall be clear and transparent for all actors in healthcare system and need to be updated on a regular basis.</p>	
Source	[12, 16, 17]

Principle #2 ERP is an important policy tool but it should be used in a mix with other tools and not as a stand-alone policy	
<p>In countries that apply ERP, the relevance of ERP differs; Many countries use ERP as the sole or main pricing policy, whereas others use it as a supportive criterion in the decision making process, and prices in other countries are jointly considered together with other criteria. One reason for this is that a country’s pharmaceutical pricing policy aims to strike the balance between several other objectives. Pricing of pharmaceuticals as governmental task does not only aim at improving access for patients through lower prices, but often has also two further objectives: Sustainability of public (and private) pharmaceutical budg-</p>	

3

A further dimension would be the perspective of providers of services (e.g. doctors or pharmacists); However, doctors act on behalf of patients and (hopefully) want to provide patients with the best possible care, they can be counted the “patient perspective”

ets and the reward for innovation. The latter one could be addressed with Health Technology Assessment (HTA) which is increasingly used by competent authorities and much progress has been made in applying those evaluations to pharmaceuticals. Usually such evaluations examine the benefits to be gained from utilising a certain medicines with respect to both patient's and the overall health care system cost. Since HTA compares the effectiveness of one intervention with another intervention it is rather a tool for making reimbursement decisions and should therefore be used as a supportive criterion for pricing.

It is also possible to consider research and development cost, provided that sufficiently detailed, comparable and reliable product-specific data relating to these costs have been submitted. However, such figures can be biased up-wards for three reasons: (1) The amount of spending in R&D activities gives no information about the efficiency of the spending. A consideration of these cost may incentivise inflated R&D expenses of product developers. (2) In the last decade pharmaceutical companies have concentrated their R&D activities on therapies of more and more narrow conditions which are generally more costly to test, as they typically require more complex patient care and monitoring, longer periods for effects to be observed or larger trial sizes to establish their efficacy. (3) Post-marketing surveillance (e.g. by registers or observational studies) and clinical trials phase IV aim to monitor a medicine's long-term effects. However, it has been criticised that the majority of these trials are designed to promote the prescription of new drugs rather than to generate scientific data done for their promotional value. Including these costs into R&D costs does not necessarily reward innovation, but marketing efforts.

With respect of applicable state aid rules and trade agreements etc., an objective which could play a minor role in the pricing decision is reward for local investment or the protection of the national medicines provision system (to avoid shortages) as this should not be addressed by health policy but rather by economic policy (e.g. tax incentives) or industrial policy (structural funds).

Source	[16, 17, 19-24]
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Principle #3

ERP is a mechanism which determines the maximum price of a medicine

Prices for pharmaceuticals can be determined in three different ways.

- Free pricing by pharmaceutical manufacturers
- Direct control of product price
- Profit Control

ERP is a policy tool that aims to determine the maximum price for a medicines and can be classified as direct control of product price. However, in literature there is often a lack of distinction between ERP, IPR and RPS, the two latter ones being rather a reimbursement tool. The reasons for this confusions may be related to the intertwining pricing and reimbursement decisions reflected by the situation that both decisions can be made by the same committee. A further cause could be the practice of some countries to apply ERP also for reimbursement purposes.

Pharmaceutical regulation is shaped by several factors like institutional settings or a government's priorities in health policy. Because of those differences, different pricing mechanisms emerged and it is acknowledged that they have proved to work for the respective countries. Countries will not be restrained from continuing to work with established procedures but they should consider that their pharmaceutical policy objectives might be achieved more efficiently. For instance, reimbursement lists usually include on- and off-patent medicines. Applying the mechanics of ERP to pricing decisions for off-patent medicines can be ineffective. As the volume of off-patent medicines as share of the total consumption of patients is usually higher than the volume of on-patent medicines, prices of more medicines have to be compared and the administrative burden may be higher. In addition, it raises questions which products are used for reference purposes. Countries that apply ERP also to the off-patent segment and have decided to use the original product in their reference country as benchmark[25] will face large price differences. E.g., in Denmark the average unit price at wholesale level of the originator Atorvastatin (DKK 1.5320) is more than 1,000 % above the average unit price of generic Atorvastatin (DKK 0.1185). Such large price variations can also be found for other medicines [26](2) Furthermore, if

ERP is used to determine the maximum price for generics it could result in result in higher price levels than in competitive markets because of lacking and in price convergence..

The prices determined through ERP can either serve as maximum prices or as starting point for further negotiations between public payers and providers of medicines. Although, the second case involves rather the competent authority for reimbursement, it would be desirable if in both cases the final result was made publicly available.

Source	[27, 28]
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Principle #4 Build up capacity in the field of price comparison

The functioning of any regulation in the area of pharmaceutical pricing (including ERP) depends on the capacity for price data collection, interpreting and understanding the gathered information, exercises to monitor and enforce respective price regulations, for a wide range of products in different strengths, forms and delivery systems.

ERP has been described as ‘a relatively simple and easy-to-apply system compared to economic evaluation, for example’. This is true insofar that ERP does not require authorities to provide for great investments in economic evaluations as they have to do for other pricing mechanisms (e.g. value-based pricing). However, it would be wrong to conclude that ERP is a simple exercise as ERP systems have high degree of complexity. Technical capacity of staff (e.g. data management, data analysis) needs to be built in order to perform the price surveys and comparisons correctly and it is crucial to have access to reliable and up-to-date price information. The efficiency of ERP is strongly related to dedication and competencies of the staff in charge of the system and the available resources.

Source	[22, 29]
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Principle #5**Implement price monitoring to improve quality and comparability of price information of pharmaceutical products**

There is a variety in the design of ERP systems used internationally to set prices of medicines. In each country ERP is applied somewhat differently, usually in combinations with other pharmaceutical policies. Due to continuing differences in institutional settings and the role of the respective institutions (e.g. competent authority for different aspects), there is no (and probably there will not be) unified ERP system but rather a range of ERP designs depending on the country specific context.

ERP has the potential to make a significant impact on the annual increase in pharmaceutical expenditure, but whether it can deliver these promises or not depends on a countries' ability and willingness to undertake regular monitoring of medicine prices in their reference countries. Measuring, understanding and monitoring medicine prices are fundamental activities if countries are to fine-tune or co-ordinate their pricing policies in order to improve both the availability and the affordability of medicines and to measure the effects of ERP. Ideally a rigorous evaluation should be done as a joint exercise by a large number of countries coordinated by an independent organisation.

Source

[16, 30, 31]

Overarching principle B: An ERP system shall be set up in a simple and manageable way to keep the administrative burden at a reasonable level.

Principle #6	MAH should be required to provide prices in reference countries but they should be confirmed through independent price search
<p>In a large number of countries that apply ERP, information about prices in the reference countries is provided by the marketing authorisation holders. Competent authorities benefit from the fact that MAH should know best at which price their product is sold in other countries. However, market structure and negotiation positions are largely shaped by information. Therefore competent authorities are advised to confirm the provided prices through independent price search. The existing EURIPID database has demonstrated that a European price database is extremely supportive for policy-makers when doing price comparisons. A coordinated price database is a big help since price search, validation and comparison for ERP is highly time-intensive and involves a lot of administrative efforts. With the help of the EURIPID database the administrative burden could be reduced to a minimum and capacity of authorities with respect to comparison of pharmaceutical prices can be improved (cf. principle # 4). Independent price search can help to reduce the information asymmetry at the time of the launch of a medicine and should be done during ERP.</p> <p>Availability of valid source of information on prices in all referenced states in the basket is a critical parameter. Transparency and validity of referenced prices is assured when the applicant (MAH) and the competent authority rely on the same reference dataset. MAHs should have the possibility to challenge determined prices through proofing their claims by documented prices. Additional invoices by the MAH can be taken into account as a proof of prices, but authorities should be aware that this procedures manifests the already existing asymmetric information and weakens negotiation position.</p> <p>Furthermore, the requirement to use commercially available sources of information which are not published by the pricing authority may pose legal and accountability issues when used for administrative decision making.</p>	
Source	[15, 17, 32, 33]

Principle #7**ERP should be preferably applied to on-patent medicines or medicines without generic alternatives at the market**

ERP is generally applicable to all types of medicines and indeed, in practice different countries apply it to different types of medicines. The effectiveness of ERP varies between different product types and in literature it has been argued, that for off-patent medicines other pharmaceutical policies, like a reference pricing system (RPS), are more efficient than ERP for regulating prices. ERP takes full effect when it is used for determining the price of medicines in monopoly market position. It has been recommended that price regulation should entail only to those medicines in the out-patient sector purchased by, or reimbursed by the State or public payer. This is justified by the goal of making an efficient use of public resources, but it does not capture two aspects: Firstly, medicines that are mainly applied in hospitals and are not necessarily included in a national positive / reimbursement list for the out-patient sector although they are paid by public payers. A number of European countries does not regulate prices of hospital medicines although some of them are quite expensive. As hospital prices serve as an anchor when MAH apply for inclusion into the reimbursement list - if they apply at all - this has been used as a backdoor to price premiums. Therefore price regulation through ERP should apply to on-patent medicines from both sectors. in-patient and out-patient.

Secondly, it emphasises the role of governments as payer, but it does not take into account the role of governments acting on behalf of their citizens to protect them from excessive out-of-pocket payments. Just because medicines are not paid by public payer, it does not mean that they are not paid at all. Costs for those therapies are shifted to the private sector which is too fragmented as being able to occupy a comparable negotiation position as governments have.

Pharmaceutical pricing regulation is very complex and the implementation of technical solutions depend on several factors like the government's policy or the size of a national market. The application of ERP to generics or biosimilars is not excluded as a possible option. Regulating the maximum price of generics through ERP while promoting competition through other generic policies (e.g. RPS) is no contradiction, but applying ERP to generics may pose methodological challenges. The potential saving also need to be carefully balanced against the danger of products leaving the market for economic reasons. The preferred scope of medicines covered by ERP should be seen in connection with the

other pricing policies that a country has at hand. In any case, it is better to use ERP than no price regulation at all.

Source [20, 28, 34, 35]

Principle #8 ERP should be preferably applied at the level of the manufacturer or producer of the medicine

Margins and taxes are different in the various countries, resulting in varying price differentials along the pharmaceutical distribution chain. Those differences cannot be attributed to the manufacturer, but to national distributors and to national policies – or in some cases the absence of the latter. Ex-factory prices for comparison eliminate issues related to differences caused by distribution mark-ups and should preferably be used for ERP.

Due to economic or geographic conditions, some countries are not able to regulate prices on ex-factory level. In such cases pharmacy purchasing prices are a more adequate choice, but regulating prices at this level is more challenging, as it needs to take more aspects into consideration. It should be accompanied by measures mitigating possible negative effects.

If reference countries publish other price types, then the calculation of ex-factory prices should preferably be done based on information about statutory distribution remuneration (e.g. wholesaler and pharmacy mark-ups/add-ons). If no statutory remuneration regulation is available, approximations resp. assumptions could be based on published average margins in this country. However, in case the average margins are unknown or not available such an assumption is not recommended.

Source [16, 31, 36]

Principle #9 The size of the reference country basket should be in line with the objectives of ERP

There is no one-fits-all approach but this is a question depending on the policy objectives that are aimed to be achieved with ERP (cf. principle #2), the relevance of the ERP in pricing (cf. principle #2) and the design of the other criteria. A consideration of those aspects should lead to the identification of a number of countries that should neither be too small, nor too large. The biggest risk in ERP use is incorrect choice of reference countries i.e. countries with substantially different market structure or prices. Major criteria defining the composition of country baskets are geographic neighbourhood, a comparable economic

situation in the reference countries (as reflected by macro-economic or other specific indicators in order to account for the ability-to-pay) and similar health system objectives and structures.

It is argued that larger baskets reduce the direct and indirect impact of individual country, will probably provide a more representative sample of prices and achieve lower prices for pharmaceuticals. However, including too many countries in the reference basket makes a system very complex to run (methodological issues about price comparisons), increases the administrative burden (collecting data) and also have impact on access to medicines.

A pre-requisite for applying ERP is the availability of valid price-information from other countries. The inclusion of countries with lower prices - which tend to have a fewer number of products on the market - can cause delays in the access to pharmaceuticals (cf. principle #12). From this perspective a balanced approach regarding the selection of reference countries in order to enable ERP and to increase the access to medicines is advisable.

Some countries have demonstrated remarkable results with smaller basket (including 7-9 well-selected countries) combined with other measures. This number keeps the administrative burden manageable while being able to contain (public) pharmaceutical expenditures. Independent of its size, the reference country basket should be reviewed periodically to ensure it still reflects the mandate of pharmaceutical pricing policy.

Source

[5, 17, 37-42]

Principle #10 The formula applied should reflect the objective of ERP

ERP is said to be rather ‘path-dependent’ as the effects will be very different depending on the choice of reference countries (cf. principle #5) and the calculation formula that defines the reference price. Like in the previous principle there is no “gold standard”, which is reflected in the large variation of formulas for the actual calculation of reference prices among European countries: 15 countries use the average price or a slightly modified method, whereas in six countries the reference price is set as the lowest price. Although one rationale of ERP is cost containment, it would be too simplistic to apply the formula of lowest price without any other considerations. Low prices in reference country can be related to (1) the ability to pay of low-income countries, (2) market size (large sales and/or orders) (3) variations in exchange rate and (4) company policies. The most adequate formula should depend on the policy objective that authorities plan to achieve and further methodological criteria (country basket, frequency of ERP activities).

Another aspect which should be considered when deciding the calculation method is the economic situation in reference countries (cf. principle #11). If countries with a lower GDP/capita are included in the reference basket, they are more likely to also calculate their pharmaceutical prices by referencing to the lowest price of yet another country. A calculation method in the form of “lowest price in the reference countries” seems only fair if the average GDP per capita of the reference country/–ies is higher than the own GDP per capita. Closely related to the choice of formula is the availability of price information, which is a pre-requisite for conducting ERP (cf. principles #9 & #12).

Data gaps on price information can occur when the product goes off-patent, i.e. generic alternatives become available. Since in some countries originator products were either withdrawn from the market or originator medicine prices were not available following their delisting from reimbursement (prices of non-reimbursable medicines tend not to be published). However, this is mainly an issue for countries that apply ERP also to generics. The important message is to carefully consider the choice of the formula in conjunction with other aspects.

Source	[16, 17, 43, 44]
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Principle #11**ERP should be seen in a broader, international context in order to avoid logic inconsistencies and to account for different abilities to pay.**

At European level, several proposals have been made in order to increase the effectiveness and accessibility as well as to improve the resilience of health systems of EU member states. With respect to pharmaceutical pricing it was suggested to give consideration to 'improved cooperation on building mechanisms for increased transparency and better coordination to minimise any unintended effects that current national pricing systems may have in terms of accessibility throughout the EU'. Although pharmaceuticals systems among European countries are different in their design, efforts in harmonising certain areas seem to be promising. With respect to ERP, one dimension of such cooperation is the broader international context of pricing. In literature, strategies are described how manufacturer respond to ERP, strategic launch decisions ("launch sequencing") being the most cited one, up to a situation in which certain pharmaceuticals are never brought to national markets during the patent exclusivity period.. Therefore national pricing and reimbursement authorities can realise headroom for improving the mechanisms by avoiding logic inconsistencies of ERP requirements and better coordinating their calculation methods. Both can be implemented by countries either unilaterally or in a collaborative approach. A collaborative approach, with a tool like the EURIPID database, however seems to have an positive impact in regard to transparency and quality of data.

Another possibility to include the broader, international context in the pricing framework is to consider information related to more 'general elements' at country level (so-called 'indirect price information'). This could include (1) economic indicators like the gross domestic product (GDP), sales volumes or purchasing power parities (PPP), (2) health system indicators like health or pharmaceutical expenditures (3) pharmaceutical system indicators like the applied methodology related to ERP, statutory discounts and the market size.

Source

[5, 17, 31, 45-47]

Principle #12 Prices determined through ERP should be regularly revised

An often faced challenge of authorities applying ERP is the non-availability of price information in reference countries. This is mainly related to the practice of launching medicines in different countries at the different points in time. Although theoretic models predict that such launch sequences should be a rare event, in practice they are not as ERP seems to incentivise marketing authorisation holders to first launch their products in high-priced countries (cf. principle #7). In countries where ERP activities are only undertaken at the market launch of pharmaceuticals, post-launch price movements cannot be considered. This has resulted in rather high price levels in some countries compared to their fellow countries with similar economic conditions. In order to improve access to medicines ERP activities should be undertaken also with few available price information, but in such systems price revisions need surely to be undertaken. This could be done on either at an ad-hoc basis as soon as a product becomes available in the reference countries (or its price changes) or on a regular basis. The frequency of those intervals needs to be balanced against the workload depending on the number of reference countries and the products subject to price revision. Intervals between 1 and 3 years are considered by authorities as sufficient, but literature and experience from authorities suggest high efficiency of annual price revisions to secure that changes in the reference countries are taken into consideration. As this require a lot more work it is recommended to monitor (cf. principle #15) and, if necessary, revise at least the prices of new and/or high cost medicines, or the 30 to 60 substances which generate the largest expenditures for public payers and patients.

When the patent protection of a medicine expires usually soon generic alternatives enter the market. Many countries have implemented the practices of setting the price of a generic in relationship to the original product medicine, usually at a certain percentage lower than the original medicine price. The design of this so-called generic price link policy may vary, with different generics and in some cases the prices of original medicines might also be part of the policy. This can results in price variations up to 922% of off-patent products at the ex-factory price level. It is possible to adjust for such variation i.e. applying ERP only to original products or comparing like-with-like but both pose further challenges like the non-availability of data (cf. principle #10). In line with previous principles, other policy mechanisms seem to be more appropriate and efficient with regard to generics.

Source	[6, 7, 43, 48, 49]
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Overarching principle C: A well-defined methodology of price survey, with clear rules, is supportive for staff doing the price surveys and comparisons, and guarantees other stakeholders (e.g. pharmaceutical industry) a higher predictability of the results.

Principle #13	Differences in the reimbursement status of medicines in the reference country should be taken into account
	<p>A major point of critique concerning ERP is, that it does neither reflect the willingness-to-pay nor the ability-to-pay.</p> <p>The discussion regarding the consideration of prices from other countries has mainly focussed on the argument importing pharmaceutical pricing policies from other countries. Despite the relevance of reimbursement decisions, the question how to deal with differences in the reimbursement status has never been addressed. Reimbursement decisions reflect priorities in health care and are – like pricing decisions – a national competence.</p> <p>By applying ERP only to reimbursed medicines, countries additionally import priorities in disease treatment from other countries. It can be questioned if this contributes to achieve the policy objectives preferred by stakeholders, competent authorities and public payers. Apart from this the question of reimbursement status is also related to the availability of price information, as in some cases only prices for reimbursed medicines are regulated and publicly available. This could affect – not only but – particularly medicines which are mainly administered in hospital settings and that are not included in price list (cf. principle #3).</p> <p>Among European countries the availability of price information for hospital medicines seems to be lower than for out-patient medicines. Therefore it is recommended to consider prices of non-reimbursed medicines but it needs to be assessed whether the price is comparable in such cases, particularly as prices of non-reimbursed medicines are not regulated and tend to be higher than regulated prices.</p>
Source	[16, 43, 50, 51]

Principle #14**When pack size is different, define a band within which different packages are considered as equal or use unit prices**

Preferably the same packages size should be taken into account however if the same pack-size is not available then two further options should be considered:

- **Percentage band** within which different packages are considered as equal. This is particularly of interest in cases of small deviations (28 vs. 30, 56 vs 60, 98 vs. 100, etc.)
- A comparison at the level of **unit prices** (e.g. per tablet, vial) is considered as an appropriate approach since it factors in all different pack sizes across countries.

A comparison of daily defined doses (DDD) is not advisable for several reasons: (1) DDD may vary between countries. The WHO Collaborating Centre for Drug statistics has developed an internationally recognised classification of ATC/DDD but for new active ingredients an ATC/DDD is not immediately available. (2) DDD are a tool for drug utilisation research in order to improve quality of drug use and also the WHO Collaborating Centre for Drug Statistics Methodology recommends against the DDD usage for pricing. (3) Using DDDs may imply the interchangeability of pharmaceutical forms which is not always justified.

Source

[18, 41, 52]

Principle #15**When packaging/container is different, countries should agree on a “comparability catalogue”**

Packaging is one of the easiest ways for market segmentation of pharmaceuticals and ERP is highly vulnerable as any change in dosage, packaging or composition of active ingredients helps the product to appear differently and poses problems of comparability. When applying ERP, priority should be given to compare the same pharmaceutical speciality, but if it is too fragmented, countries should agree which containers are considered as equal. Such an agreement should also clearly specify the exemptions where the differences in containers are considered to result in significant differences for patients.

In order to take account for Commission Regulation (EC) No 1234/2008 it is suggested that MAHs should demonstrate that different containers result in significant differences in production costs.

Source

[18, 53, 54]

Principle #16**When the pharmaceutical form (tablets vs. capsules vs. film-coated-tablets etc.) is different, countries should follow clinical practice**

Medicines vary according to the route of administration and can be distinguished into several groups, each group with further subgroups of pharmaceutical forms. Both, route of administration and pharmaceutical form, have an influence on the pharmacokinetics and pharmacodynamics. Pharmacodynamics examines which effects an active ingredient has on processes within the human body, whereas pharmacokinetics examines how the human absorbs and distribute a medicine. Under the premise of comparing things that are comparable pharmacokinetics and pharmacodynamics can be restricting. From this perspective tablets and capsules would be comparable, but a prolonged release tablet would be a different product.

The other end of the spectrum is the view to consider for each medicine that can be administered for the same indication the cost of therapy. However, this neglects issues related to the extent of harmonisation of treatment guidelines. There are more than 400 individual recommendations for prevention and treatment of cardiovascular diseases. Treatment of certain indications vary from individual to individual due to personal characteristics (e.g. sex, weight) making it difficult to determine standardised treatment cycles. It is possible to use the unified summary of product characteristics (SPC) provided by the European medicines agency (EMA) as starting point for calculations, many medicines authorised by national agencies still circulate in Europe with different and often divergent SPC.

With respect to comparison of different pharmaceutical forms during pricing procedures it is recommended that pricing authorities should follow clinical practice. Whenever doctors within a country do not have any reservations of switching during a therapy of an indication between different pharmaceutical forms, then why should pricing authorities hesitate to apply ERP to medicines of different pharmaceutical forms if price information of the same pharmaceutical form is not available.

Source

[55–58]

Principle #17

The choice of exchange rate when applying ERP should reflect the objective of the pharmaceutical pricing policy

Prices determined by ERP are subject to significant exchange rate fluctuations and the choice of exchange rates has been quoted as a contributing factor to the effectiveness of ERP. This affects particularly countries that do not share a currency (e.g. Euro) or have countries with other currencies in their reference basket. Problems with regard to patient's access can occur in both directions: If the exchange rate of a country depreciates, the import of medicines gets more expensive and causes problems in the affordability of medicines. If the exchange rate of country appreciates there is an incentive to export medicines and which could result in shortages. A regular review of prices determined by ERP seems to be the best approach not only to account for missing price information during ERP (cf. principle #9) but also to account for exchange rate fluctuation. A major critique on this procedures is that regular revised pharmaceutical prices depend stronger on the macroeconomic indicators in reference countries. Therefore the choice of exchange rate plays a crucial role and has to be balanced between equalising short-term fluctuations and not too long periods. By using daily exchange rate could be rather driven by statistical outliers while averages of a medium-term period are more robust against fluctuations. Quarterly or biannual or yearly exchange rates appear to be appropriate, as exchange rates of longer time periods can help in avoiding the effects of exchange rate fluctuations.

A further option related to exchange rate which can be considered is the use of a **common denominator currency** for comparison to avoid cross-exchange rates (e.g. from currency A to currency B and then to currency C). However, it appears appropriate in cases when no direct exchange rates (e.g. from currency A to currency C) are available. The exchange rates of the European Central Bank (ECB) should be preferably be used as the ECB provides the most comprehensive records on exchange rates in Europe and feature a long record of data.

Since regular price revisions have more impact in the first years it could be an option to set longer revision intervals after prices have settled down i.e. price information from all countries is available.

This challenge with price comparisons under exchange rate fluctuation once more underlines the reasonability to apply other approaches to generics (e.g. RPS).

Source

[14, 19, 59]

Main messages/ Future avenues/ Outlook

This report aimed to derive evidence-based best-practice principles for the application of ERP. National pharmaceutical regulation on pricing and reimbursement emerged from the respective institutional, social and political context. This has resulted in a large array of pharmaceutical pricing and reimbursement system in European countries. This report does not question the national competency for pricing and reimbursement but rather suggests areas in which headroom for improvement exists. From literature and interviews information about different pricing systems and their effects have been gathered, which build the basis for the development of the best-practice principles for ERP.

Objectives and methods of pharmaceutical pricing systems should be clearly stated and reviewed periodically. Pharmaceuticals pricing policies usually aim to strike the balance between several objectives. Policy makers should clearly state which objectives their pharmaceutical policy pursue and if certain aspects are prioritised – preferably also in line with other areas of the health system. Furthermore, underlying principles and applied methods of pricing shall be clear and transparent for all actors in the health system. This would be supportive for the technical staff doing price surveys and comparisons, but also guarantees other stakeholders a higher predictability of the results. Objectives and methods should be subject to regular revisions as framework conditions in health systems can change drastically within short periods of time (e.g. the arrival of direct-acting antivirals for the treatment of Hepatitis C or HIV).

An ERP system shall be set up in a simple and manageable way to keep the administrative burden at a reasonable level. The application of ERP is not as straightforward as it seems but can pose methodological challenges during price comparisons which need to be addressed. From this perspective, it seems that ERP is most appropriate for pricing of on-patent medicines or medicines without generic alternatives on the market. An application to off-patent medicines is possible but a demanding task in terms of time and design (e.g. data gaps, reference product, exchange rates). The size of the reference basket and the formula applied have the most influence on price level as well as on the availability of medicines and should reflect the prior defined objectives of ERP.

ERP should be seen in a broader, international context in order to avoid logic inconsistencies and to account for different abilities to pay. A problem associated with pricing and reimbursement being as national domain is to lose the bigger picture, which is reflected in some logically contradictory calculation methods. Align with recommendations of previous reports

and communicates more co-ordination and co-operation between countries should be considered. In some areas (e.g. exchange of price information) this has co-operation is already advanced and proofed to be fruitful. Another important area which would facilitate the process of ERP would be a mutual agreement on a “comparability catalogue”: Packaging and product presentation is one of the easiest ways for market segmentation of pharmaceuticals and ERP is highly vulnerable to such segmentation, as any change in dosage, packaging or composition of active ingredients helps the product to appear differently.

The increasing asymmetric distribution of information due to confidential agreements benefits only the party which possesses this information. The EURIPID price database is good example for one area of co-operation as sharing price information has facilitated the process of ERP for technical staff that conducts comparisons. However, ERP faces two major challenges: The first one is the availability of price-information as pre-requisite for conducting price comparison in the first place. This has already been covered in the principles above. The second – and more recent one – is deviation of real prices from list prices. Undisclosed rebates or other comparable arrangements result in inflated prices and – as a consequence – in unreliable price benchmarks. Depending on the objectives of ERP, this is not necessarily a limitation. If countries set prices as maximum price and negotiate lower real prices with the manufacturer, then it is perfectly fine to use such prices. However, this procedures increasingly obscure prices and bias the distribution of information in favour of the pharmaceutical manufacturer. Economic theory suggests, that from a segmentation on the demand side i.e. public payers, mainly the supply side i.e. pharmaceutical manufacturer, improves its negotiation position but that the end-user, i.e. the patient does not necessarily benefits.

From this perspective the increasing use of MEA has to be judged critically, as way to re-segregate the demand side. MEA are concluded between public payers and producers to reduce the financial risk for both due to the uncertainty surrounding the introduction of a new medicines. Although MEA can take different forms, the majority of MEA are non-outcome based, suggesting that MEA are a “work-around” expression for confidential discounts⁴. The prevalence of non-outcome based MEA is argued with the lack of capacity to monitor outcomes by authorities e.g. the management of registries. Independent of those arguments, confidentiality clauses of MEA result in further fragmentation on the demand side, which was the reason for co-operation like the exchange of price information, in the

⁴ An evaluation of the use of manage entry agreements among Austrian hospital pharmacists who are responsible for pharmaceutical procurement have shown that among those persons there is a lack of distinction between those two different concepts [60].

first place. Governments and competent authorities should think if weakening their negotiation position is worth the price and, should promote transparency by sharing health and medicines information.

Finally, there is no indication from literature that well-managed ERP systems with clear-cut and workable rules, that are embedded in the national health care and pharmaceutical policy framework yield non-manageable negative aspects on the affordability of medicines to patients.

In the contrary, countries with price regulations (including ERP) tend to have lower prices than countries without price regulations. Problems related to the availability of medicines, because they are put back in the launch sequence – or are even never brought to the market during market exclusivity at all – is not only related to prices. Other contributing factors are (1) different data requirements in national reimbursement dossiers, (2) additional information request or the results of new studies or (3) the limited capacity to make submissions and therefore prioritise submissions by market according to their expected profitability [61].

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