

Impact of changes in the methodology of external price referencing on medicine prices: discrete-event simulation

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Abstract

Background: Several governments apply the policy of external price referencing (EPR), which considers the prices of a medicine in one or more other countries for the purpose of setting the price in the own country. Different methodological choices can be taken to design the EPR policy. The study aimed to analyse whether, or not, and how changes in the methodology of EPR can impact medicine prices.

Methods: The real-life EPR methodology as of Q1/2015 was surveyed in all European Union Member States, Iceland, Norway and Switzerland through a questionnaire responded by national pricing authorities. Different scenarios were developed related to the parameters of the EPR methodology. Discrete-event simulations of fictitious prices in the 28 countries of the study that had EPR in place were run for a period of 10 years. The continuation of the real-life EPR methodology in the countries as surveyed in 2015, without any change, served as base case.

Results: Consideration of discounts (an assumed 20% discount in five large economies and the mandatory discount in Germany, Greece and Ireland) and determining the reference price based on the lowest price in the country basket would result in higher price reductions (on average -47.2% and -34.2% compared to the base case). An adjustment of medicine price data of the reference countries by purchasing power parities would lead to higher prices in some more affluent countries (e.g. Switzerland, Norway) and lower prices in lower-income economies (Bulgaria, Romania, Hungary, Poland). Regular price revisions and changes in the basket of reference countries would also impact medicine prices, however to a lesser extent.

Conclusions: EPR has some potential for cost-containment. Medicine prices could be decreased further if certain parameters of the EPR methodology were changed. If public payers aim to apply EPR to keep medicine prices at more affordable levels, they are encouraged to explore the cost-containment potential of this policy and to take appropriate methodological choices in the design of EPR.

Background

Access to affordable medicines is a key policy objective in all countries of the world, and it has also been defined in the Sustainable Development Goals (1). Medicine prices are one important determinant to ensure affordable and equitable access to medicines (2). Affordable prices are of relevance both for patients who have to purchase medicines fully out-of-pocket or co-pay to the medicine price as well as for public payers (e.g. a social health insurance, a national health service) that cover (parts of) pharmaceutical expenditure. While the reduction in out-of-pocket payments for medicines lowers the risk for impoverishment of households (3-5), savings in public pharmaceutical budgets allow public payers to treat in total more patients and to contribute to the financial sustainability of the health care system (6).

To achieve affordable medicine prices, governments can employ a mix of pharmaceutical pricing policy options (7). A policy to set medicine prices that is increasingly being used is external price referencing (EPR). Applying this policy, the pricing authority or public payer considers the prices of a medicine in one

or more other countries in order to derive a price benchmark for the purposes of setting or negotiating the price of a medicine in the own country (8). Meanwhile, EPR has been implemented in many high-income countries and also in middle-income countries (9-11). Some countries without price regulation that aim to introduce price control have also opted for EPR as the primary pricing policy (12).

While, in principle, EPR can be applied for all kinds of medicines, it is, in practice, mainly used for pharmaceuticals with a new active substance that have no equivalent medicine on the market. It is sometimes supplemented by further policies if public payers consider the EPR-based benchmark price unaffordable or unacceptable. In such cases, the payer and the pharmaceutical company tend to follow up by negotiating a lower price, which may, or may not, be linked to specific conditions (e.g. capping of the number of patients treated, price-volume agreements or clinical outcomes in pay-for-performance arrangements). In Europe, such arrangements are referred to managed-entry agreements (MEA) (13). The extent of discounts granted by industry to the payers, and thus the actual net prices are, as a rule, kept confidential in the MEA (14). This has an impact on other EPR-applying countries which, due to non-disclosure of discounts, have to refer to the officially published, thus higher, list prices for their EPR calculations (15, 16).

Apart from the referencing to list prices, which is a reality in nearly all EPR-applying countries, other methodological choices of EPR vary between countries. For instance, in 2018, 18 of the 41 Pharmaceutical Pricing and Reimbursement Information (PPRI) countries^[1] that applied EPR used the average or median of the prices in other countries, while 9 countries referred to the lowest prices and the remaining countries applied other algorithms to determine the benchmark prices. 20 EPR-applying PPRI countries had a basket of fewer than ten reference countries, whereas five PPRI countries reference to all or nearly all other EU Member States (12).

Overall, evidence on the impact of pharmaceutical pricing policies is still lacking (17, 18). Some studies showed that the introduction and implementation of EPR has contributed to lower medicine prices and/or savings in the public budgets (19-24). Other research, however, pointed to the inferiority of EPR's ability as cost-containment tool compared to other pricing policies, such as value-based pricing, or showed inconclusive results (25-28).

The effects always also depend on its design of a policy, and policy-makers have thus been urged to take appropriate methodological choices for EPR (17, 29). However, there is lack of information on the cost-containment potential of the different parameters that make up the EPR policy. It has been suggested to tentatively assess the impact of EPR by modelling and scenario-building approaches (30).

Against this background, the paper aims to analyse the impact that the EPR methodology can have on medicine prices. The findings are intended to provide evidence to policy-makers who plan to introduce, or adapt, EPR.

The study analyses solely EPR; the policy of internal price referencing is not scope of this research. Internal price referencing considers the prices of comparable medicines (e.g. of the same active

ingredient or therapeutically equivalent medicines) in the same country and is typically applied for medicines in the off-patent market (e.g. generics, biosimilars, and originator medicines whose patent has expired). Furthermore, the study is limited to the cost-containment potential of EPR as it investigates medicine prices as outcome parameter, and it does not consider other policy objectives (e.g. timely access to medicines, incentives to pharmaceutical industry, and fairness in access to medicines across countries) that policy-makers may aim to achieve. The study neither advocates in favour or against the use of EPR but aims to explain possible implications of its methodological design on medicine prices.

[1] PPRI is a network of pharmaceutical pricing and reimbursement authorities in 47 countries, including all 28 Member States of the European Union and further countries in Europe (e.g. in the Balkans) and Central Asia as well as Canada, Israel, South Africa and South Korea.

Methods

The study simulates the impact of existing EPR methodologies on medicine prices after ten years and compares these findings to results in cases of changes in EPR parameters.

'No change' base case

The base case describes the methodology of EPR as in place in the EPR-applying countries of the European Union (EU) and the European Economic Area (EEA) in the year 2015. 25 EU Member States (all except Denmark, Sweden and United Kingdom) and the EEA countries Iceland, Norway and Switzerland were included (a total of 28 countries).[2]

The details of the EPR design with regard to reference countries, determination of the benchmark price, consideration of discounts, weighting of price data in other countries and frequency of revisions were surveyed in the studied countries. Based on literature and previous surveys done in the field (as part of information sharing activities in the PPRI network of competent authorities (31)), the authors drafted a description of the EPR methodology for all included countries and asked the respective pricing authority in the first quarter of 2015 to review and validate the information for their country.

Simulation scenarios

Simulations were run for assumed (not real) prices (ex-factory price level) for a period of ten years (120 months). To kick-off, a launch price of 100 euro was assumed for Germany (as empirical evidence points to Germany being a first launch country in many cases (32, 33)) and of 70 euro for Italy. Prices based on EPR would only be determined after the prices in the defined (minimum) number of reference countries were available.

Prices were held constant until a re-evaluation was due according to legislation. No price deflation or inflation was considered. Exchange rates were assumed constant across time.

Seven scenarios were developed based on assumed changes in the parameters of the EPR methodology (Table 1), for which simulations were run.

[2] Sweden and United Kingdom do not apply EPR at all, and Denmark does not use EPR for price setting purposes in the outpatient sector. Liechtenstein was excluded because it applies the prices of Switzerland.

Results

Real-life EPR methodology

The survey of the EPR methodology applied in the studied countries had a 100% response rate following persistent reminders. Variation in the EPR methodology was observed particularly related to the number of reference countries: While Luxembourg considered the prices of solely one country, Hungary and Poland had 31 countries in the reference basket. In most surveyed countries the reference basket included eight to 15 countries. In some countries (e.g. Italy, Spain) the number of reference countries was not explicitly defined but a larger group of countries (e.g. those from the Euripid database or the Euro zone) served as reference. Differences were also found with regard to the method to determine the reference price (average or minimum of the prices in the reference countries, or a combination, or a slightly different other calculation method[3]). Several EPR-applying countries reviewed their prices bi-annually and annually, but some countries have not provided for any revision in legislation. Except for Germany, in 2015, none of the countries had legislation in place to take into account discounts (not even published mandatory discounts) or to weigh price data of other countries (Table 2).

Simulations

Table 3 shows the results from different scenarios, informing about the changes in the prices achieved following a change in a parameter of the applied EPR methodology compared to the base case ('no change').

Out of all scenarios, discounted prices had the highest impact, in particular when a 20% discount was assumed for five large economies in addition to the consideration of statutory discounts: in this case (scenario 5), the achieved prices were, on average, 47.2% lower than the base case prices. In scenario 4 (solely statutory discounts considered), the average reduction amounted to 26.8%. Simulated medicine prices of scenario 4 were 55% lower than base case prices in some countries (Bulgaria, Greece, Italy, Romania, Slovakia and Spain), and simulated prices in scenario 5 were 50% lower in the majority of the countries (around 80% in Croatia and Lithuania).

A considerable effect was also shown for a changed calculation methodology when all analysed countries referenced to the lowest price in the reference countries: on average 34.2% lower than the base case prices.

Bi-annual price reviews would also lead to lower prices on average and in all studied EPR-applying countries, but to a lower extent (less than 1 per cent in several countries).

Weighting price data of the reference countries by PPP showed mixed results: medicine prices of lower-income countries would be reduced, while the adjustments would lead to higher prices in high-income countries. In particular, prices in Switzerland and Norway would increase by 40% and 18% respectively, whereas Bulgarian, Romanian and Hungarian prices would decrease by 53%, 51% and 49% respectively. After ten years, PPP-adjusted prices would be, on average, 16% lower than base case prices.

Findings differed with regard to the assumed reference countries: while a low number of reference countries resulted in lower medicine prices (except for a few countries), in several countries a large basket would rather lead to higher prices compared to the base case.

[3] The price regulation in Latvia, for instance, states that Latvian medicine prices should be third lowest of the basket of a total of seven reference countries but not be higher than the price in Lithuania or Estonia.

Discussion

The findings strongly suggest that the methodological design of the EPR policy has an impact on the intended outcomes, i.e. the medicine prices in the own country. In particular, the simulations run in this study point to considerable relevance of some of the parameters of the EPR methodology and thus the findings add to a few studies that suggested EPR's ability of reduce medicine prices (19–24).

It has been highlighted in literature (28, 34–36) and policy debate that the cost-containment capacity of EPR is strongly impaired by the referencing to 'fake prices' (37) since the real prices are not known due to the confidential character of discounts and managed-entry agreements. Both scenarios of this study that considered discounts confirmed the loss of saving opportunities due to the discounted prices in other countries. Even the scenario that only took into account statutory (thus published) discounts highlighted important price-reducing potentials. As the consideration of published discounts would not imply any breach of confidentiality, an EPR-applying country could implement it rather swiftly. In fact, since its medicine pricing reform of 2017 price data reduced by statutory discounts are taken into consideration in Austria (38). Another technical option for governments to account for discounts could be to follow the example of scenario 5 and to assume a 'reasonable' discount. At political level, a debate on price transparency is on-going, as evidenced by the 'WHO Transparency Resolution' adapted by the World Health Assembly in May 2019 that calls for disclosure of net prices as well as research and development costs for medicines and vaccines (39).

Referencing to the minimum will likely drive prices down, and this was, not surprisingly, confirmed by the simulation results. The base case scenario included some European countries that calculated their

reference price based on the average of the prices in the reference countries, and particularly for these countries, major decreases compared to the base case were seen. However, it can be discussed whether, or not, a policy of a 'race to the bottom' is an intended objective of EPR that is a pricing policy usually applied for new medicines. As an alternative, opportunities for savings could rather be achieved from off-patent medicines, as evidence on the price-reducing character of generic competition (40–44) and of tendering (45–49) is available.

The selection of the reference countries is a key decision point in the design of EPR. The WHO Guideline on Country Pharmaceutical Pricing Policies recommends choosing reference countries based on economic status, pharmaceutical pricing systems in place, the publication of actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease (17). There are two major choices to make: the size of the basket and the countries included. With regard to the latter, it is common sense that a focus on lower-priced reference countries will eventually lead to lower prices. There is, however, the risk that particularly in the beginning price setting might be difficult because medicines might not have a price and be marketed in lower-priced countries due to strategic launches of pharmaceutical companies in response to the widespread use of EPR (32, 50, 51). Thus, countries, particularly those referring to lower-priced countries, are advised to have a mechanism in place which ensures finalising price setting even in early phases (e.g. alternative countries) and provides for regular price reviews to benefit from price decreases in the reference countries over the years (see also findings of scenario 7) (18). As a related aspect, it has to be decided whether, or not, there is a need to have large country baskets. This has also to be seen in connection with the resources required for surveying medicine price data to perform EPR, which can be substantial in case of large country baskets (52). In any case, the study findings confirm the importance of a strategic selection of the reference countries: a well-chosen small country basket is not only less resource-intensive but may also achieve lower prices. Indeed, the simulations showed that most countries would pay higher prices (increases by 20% in several cases) if they used a larger basket (scenario 2). The fact that the four countries' basket (scenario 1) did not translate in substantial price decreases compared to the base case suggests that several of the countries apply a basket that appears to serve well their objectives.

EPR has been criticised for failing to deliver equity since it does not consider the different income levels of the reference countries (27, 53). As a solution, differential pricing – a policy in which medicine prices are set in line with the countries' economic status – has been proposed (54–57). Usually, differential pricing and EPR are considered as a mutually exclusive policy options. However, in the authors' perception, this is not necessarily the case. For instance, the prices in the reference countries could be weighted by indicators that reflect the economic situation of these countries (e.g. gross domestic product, PPP). The simulation scenario that was run on PPP-adjusted prices (scenario 6) showed lower prices for lower-income countries but also an increased burden due to higher prices for higher-income countries. While accounting for countries' income would contribute to more equity and fairness, such an approach may still not be politically acceptable for high-income countries that are meanwhile increasingly struggling with the affordability of medicines.

The authors acknowledge that the study has some limitations. For simplicity, EPR was assumed to be the sole pricing policy in the EPR-applying countries while, in practice, further policies may be used. No scenario of weighting the price data by volume was run because these data were not available. In practice, governments frequently lack consumption data of the other countries. A possibility could be a weighting by volume data of the own country, but even these data are not always completely accessible in some countries (e.g. in countries with a fragmented health care system, such as Austria and Germany, aggregated consumption data for the hospital sector are missing), and they lack in particular for newly launched medicines.

The analysis only focused on the outcome indicator of medicine prices. Pharmaceutical prices are indeed a major determinant with regard to affordable and equitable access to medicines (2) because in solidarity-based systems such as those of the studied countries lower prices allow the public payers to treat more patients for the same amount spent. Nonetheless, while pursuing a cost-containment approach governments are reminded that pharmaceutical expenditure is the result of price and volume components. Thus, even if prices were decreased, expenditure may grow due to increases in consumption (19). The latter may result from adjustments of previous under-use as well as possible over-use or inappropriate use.

In addition, there might be further pharmaceutical policy objectives that a government may want to achieve, e.g. to support local industry, to incentivise research-oriented pharmaceutical industry to invest in research and development or to ensure that the same price for a medicine is charged in all pharmacies throughout the whole country. Other pharmaceutical (pricing) policies might be more appropriate to reach these objectives. In addition, a government might like to achieve a mix of objectives, and this requires a mix of pharmaceutical policies.

Finally, taking a broader, more global health system perspective, spillover effects of EPR that impact access in other countries (e.g. launch delays) have to be acknowledged (11, 50, 51).

Conclusions

The study points to the importance of a careful design of the EPR policy. The findings suggest that the methodological choices taken for the implementation of this pricing policy can result in – partially substantial – changes in the medicine prices of an EPR-applying country. Consideration of discounts and the application of the lowest price (instead of the average of prices) in the reference countries represent methodology parameters with the highest ability to decrease medicine prices.

The research has important policy implications: If pricing authorities and public payers decide to apply EPR with the (exclusive) aim to achieve lower prices, they are encouraged to optimise its use by taking appropriate methodological choices when they develop and adjust their country's EPR policy by considering the learnings of the study with regard to differences in impact as for the parameters of the EPR methodology.

Abbreviations

EEA	European Economic Area
EPR	External price referencing
EU	European Union
HTA	Health technology assessment
MEA	Managed-entry agreement
PPP	Purchasing Power Parities
PPRI	Pharmaceutical Pricing and Reimbursement Information
UK	United Kingdom
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SV, PS and LL jointly designed the study concept and design. PS had the lead in surveying the parameters of existing EPR systems, supported by SV and LL. LL worked on the development of the discrete-event simulation model and ran the simulations. SV wrote the draft manuscript and revised and finalised it after reviews by PS and LL. All authors read and approved the final manuscript.

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Tables

Table 1: Simulation scenarios - assumed changes in the EPR methodology

No.	Input parameter	Scenario: assumed change in the design of the EPR methodology
1	Reference countries	All EPR-applying countries have four reference countries: Germany, Italy, Finland and Portugal. This country basket represents a mix of high-, middle- and low-priced countries.
2	Reference countries	All EPR-applying countries have a basket of 30 countries.
3	Calculation method	All EPR-applying countries reference to the lowest price of the reference countries.
4	Discounts	All EPR-applying countries consider the statutory manufacturer discounts ¹ in Germany, Greece and Ireland.
5	Discounts	All EPR-applying countries consider the statutory manufacturer discounts ¹ in Germany, Greece and Ireland and an additional assumed 20% (confidential) discount on the referenced prices in five large economies (Germany, France, Italy, the Netherlands, Spain and UK).
6	Income adjustment	All EPR-applying countries weight the price data of the reference countries by Purchasing Power Parities (PPP).
7	Revision frequency	All EPR-applying countries review the price data of the reference countries every six months and subsequently adjust of the medicine prices in the own country.

¹In addition to commercial, typically confidential discounts that a pharmaceutical company grants to a public payer, a few countries charge statutory discounts: In these cases, the amount of the discounts that manufacturers have to grant to the public payers is published in legislation (Germany, Greece) or in a framework agreement (Ireland).

Table 2: Parameters of the EPR methodology in the studied EPR-applying countries, 2015

Country	Reference countries ¹	Benchmark price	Consideration of discounts	Weighting of price data	Revision frequency (months)
Austria	26 (14)	Average	No	No	No revision
Belgium	27 (1)	Average	No	No	No revision
Bulgaria	17 (1)	Minimum	No	No	6
Croatia	3 out of 5 ² (2)	Average	No	No	12
Cyprus	4 out of 10 ² (1)	Average	No	No	12
Czech Republic	19 (3)	Average of 3 lowest	No	No	36
Estonia	3 (1)	Minimum	No	No	12
Finland	29 (1)	Average	No	No	60
France	4 (1)	Average	No	No	60
Germany	15 (1)	Average	Provided for in legislation ³	Provided for in legislation ³	No revision
Greece	26 (3)	Average of 3 lowest	No	No	3
Hungary	31 (3)	Minimum	No	No	No revision
Iceland	4 (3)	Average	No	No	24
Ireland	9 (1)	Average	No	No	36
Italy	25 ⁴ (1)	Minimum	No	No	24
Latvia	7 (1)	Third lowest price	No	No	24
Lithuania	8 (1)	Average	No	No	12
Luxembourg	1 (1)	Minimum	No	No	12
Malta	12 (3)	Average	No	No	18
Netherlands	4 (2)	Average	No	No	6
Norway	9 (1)	Average of 3 lowest	No	No	12
Poland	31 (1)	Average	No	No	24
Portugal	3 (1)	Average	No	No	12
Romania	12 (1)	Minimum	No	No	60
Slovakia	27 (1)	Average of 3 lowest	No	No	6
Slovenia	3 (1)	Minimum	No	No	6
Spain	18 ⁵ (1)	Minimum	No	No	12
Switzerland	6 (1)	Average	No	No	36

¹ In bracket the number of minimum reference countries that are required in legislation to determine an EPR benchmark price (used as input for the simulations).

² 3 (Croatia) and 4 (Cyprus) defined reference countries, respectively, out of a pool of 5 (Croatia) and 10 (Cyprus) reference countries, as data of alternative reference countries are considered in the case of non-availability of data in the primary 3 or 4 reference countries

³ According to legislation, Germany can consider both mandatory and confidential discounts of prices in other countries, but this is not applied in practice. Furthermore, Germany may weight the price data by estimated yearly turnover of the medicine (information to be provided by the pharmaceutical company) and PPP. As both discounts as well as weighting are no common practice in the EPR in Germany, this was not considered in the base case simulations.

⁴ countries with price data included in the Euripid database

⁵ Eurozone countries

Table 3: Change in medicine prices, expressed in per cent, as a result of the application of a defined EPR methodology (scenarios of a change in one EPR parameter) after ten years, compared to the base case ('no change')

Parameter Scenario	Reference countries		Calculation method	Discounts		Income adjustment	Revision frequency
	1	2	3	4	5	6	7
Austria	0.0	-9.6	-25.5	-1.5	-12.8	-6.2	-18.6
Belgium	0.0	-9.6	-25.5	-1.5	-12.8	-5.4	-18.6
Bulgaria	-3.6	19.9	-21.9	-59.0	-72.9	-53.0	-0.7
Croatia	4.0	13.6	-26.1	-40.9	-83.2	-39.4	-3.1
Cyprus	-10.5	-2.2	-35.1	-15.3	-36.5	-22.2	-5.4
Czech Rep.	-3.1	19.9	-19.7	-52.6	-50.0	-35.0	-0.7
Estonia	-3.1	19.9	-20.0	-53.1	-54.3	-27.7	-0.7
Finland	-5.1	3.7	-33.0	-23.5	-52.7	10.7	-5.0
France	-6.4	2.4	-33.5	-27.1	-58.0	0.7	-3.0
Germany	-1.5	-4.5	-12.5	-1.8	-19.1	-10.1	-10.2
Greece	-3.6	19.9	-21.9	-58.3	-68.6	-17.1	-0.7
Hungary	0.0	0.0	0.0	0.0	-20.0	-49.1	-0.7
Iceland	-17.1	-9.2	-38.4	-4.4	-18.0	3.5	-4.5
Ireland	-13.5	-5.5	-35.7	-9.4	-33.6	-7.0	-7.4
Italy	-3.6	19.9	-21.9	-59.0	-66.9	0.0	-0.7
Latvia	-3.6	19.9	-21.9	-52.6	-50.7	-32.7	-0.7
Lithuania	9.8	20.1	-20.4	-40.8	-80.5	-39.8	-0.9
Luxembourg	-28.2	-10.7	-25.5	-1.5	-12.7	1.8	-18.6
Malta	2.1	11.5	-25.6	-29.7	-66.6	-26.6	-2.0
Netherlands	-15.7	-7.7	-31.0	-6.5	-32.1	-8.0	-8.0
Norway	-24.2	-6.1	-35.8	-9.2	-39.9	18.3	-13.0
Poland	8.9	19.3	-22.5	-38.2	-76.8	-42.5	-1.1
Portugal	-1.5	7.4	-28.6	-28.0	-71.6	-28.3	-3.8
Romania	-3.6	19.9	-21.9	-62.0	-73.6	-50.9	-0.7
Slovakia	-3.6	19.9	-22.4	-58.0	-65.3	-32.7	-0.7
Slovenia	-17.9	2.1	-23.4	-15.5	-60.9	-28.3	-6.9
Spain	-3.6	19.9	-20.3	-57.6	-58.6	-10.7	-0.7
Switzerland	-17.1	-9.5	-33.0	-5.4	-29.0	39.2	-7.0
<i>Average</i>	<i>- 6.5</i>	<i>+ 5.3</i>	<i>- 34.2</i>	<i>- 26.8</i>	<i>- 47.2</i>	<i>- 16.0</i>	<i>- 5.8</i>

Rep. = Republic

The assumptions of the scenarios are described in Table 1.

Changes (decreases / increases) exceeding 25% are marked in bold.