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# IMPLICATION OF EXTERNAL PRICE REFERENCING ON PHARMACEUTICAL LIST PRICES IN EUROPE

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## INTRODUCTION

In Europe, one of the most frequently applied pharmaceutical price-control measure is external price referencing (EPR) [1]. EPR is implemented slightly differently among European countries [2].

Previous studies have shown that EPR can be an effective policy tool in reducing drug prices in Western European (WE) countries [3]. EPR is relatively simple to implement and there is a broad experience in using it, hence EPR has become a main criterion for price setting of new medicines in many European countries.

Despite the observed price reducing effect in WE countries, EPR might contribute to an opposite effect in less affluent countries in Central and Eastern Europe (CEE). This research investigated the implications of EPR on pharmaceutical list prices across Europe based on three key research objectives:

1) calculate and compare the price corridors for pharmaceuticals and non-pharmaceutical services;
2) determine the influence of EPR on pharmaceutical prices
3) determine the influence of EPR on pharmaceutical prices taken into account the effect of other potential factors

## METHODS

Price data on 21 pharmaceuticals and 17 non-pharmaceutical services were collected in order to calculate the price corridor for 7 countries, namely Bulgaria, Czech Republic, Germany, Hungary, the Netherlands, Romania and Slovakia. Data was gathered through sending out a survey to experts in each country. Pharmaceuticals and non-pharmaceutical services were selected based on their clinical relevance in Europe, representation of several therapeutic areas and portfolio of products in a previous study with similar methodology in a different geographical location [4]. To define price corridors, relative values were calculated by taking maximum and minimum prices for each product and service. These prices were divided by their average price in seven countries. The mean of these relative values were used as the price corridors' lower and upper boundaries of pharmaceutical products and non-pharmaceutical services.

For the multivariate regression analyses, relative prices were used as outcome variable. To increase the statistical power of our analysis, pharmaceutical price-data from an additional 8 countries, namely Austria, Belgium, France, Greece, Italy, Lithuania, Poland, Spain were collected using the EURIPID database, provided by the Hungarian Health Insurance Fund Administration on a statistical level.

To define explanatory variables for the multivariate analyses, data on EPR methodology in the 15 countries were extracted from a recent European Commission report [5]. Information was obtained on 4 EPR attributes: number of referenced countries, number of other EU countries referencing an individual country, rule of calculating the reference price and rule of price revision. Other factors potentially influencing pharmaceutical prices were included in the analyses: countries' wealth as GDP per capita, market potential as population size and health status as life expectancy.

Univariate regression analyses were applied to test the effect of explanatory variables on pharmaceutical prices. Robust standard error estimation was taken into account clustering the data by countries. T test was used for testing the significance of model coefficients. A significance level of 0.05 was considered throughout the analyses.

To determine the effect of different features of EPR when other factors are taken into account, a multivariate regression analysis was conducted. The final regression model was designed taking into account the correlation and multicollinearity among explanatory variables.

Certain degree of non-linearity was observed in case of two variables: number of referenced countries and number of other countries referencing an individual country. Therefore our assumption was to use quadratic curves instead assuming linearity. By using quadratic terms it can be expected that these explanatory variables do not have the equal effect on the outcome variable if the value of the explanatory variable change.

| Variables | Type | Definition |
|---|---|---|
| **Number of referenced countries** | Quadratic | Squared actual number per country |
| **Number of other countries referencing an individual country** | Quadratic | Squared actual number per country |
| **Rule of calculating the reference price** | Binary | Calculation of lowest/average of lowest price or not |
| **Rule of price revision** | Binary | Revision is applied within 5 years or not |
| **GDP per capita** | Continuous | Per €1 000,- |
| **Population size** | Continuous | Per 1 000 000 inhabitants |
| **Life expectancy** | Continuous | Years |

*Table 1. List of explanatory variables for univariate and multivariate analyses.*

## RESULTS

*Price corridor*

The price corridor was narrower for pharmaceuticals (79%-144%) compared to non-pharmaceutical services (28%-252%) in the 7 studied countries. Compared to the variability of GDP per capita, the price corridor of non-pharmaceutical services was similar or even greater, however, pharmaceutical prices had much lower variability especially in the lower end.

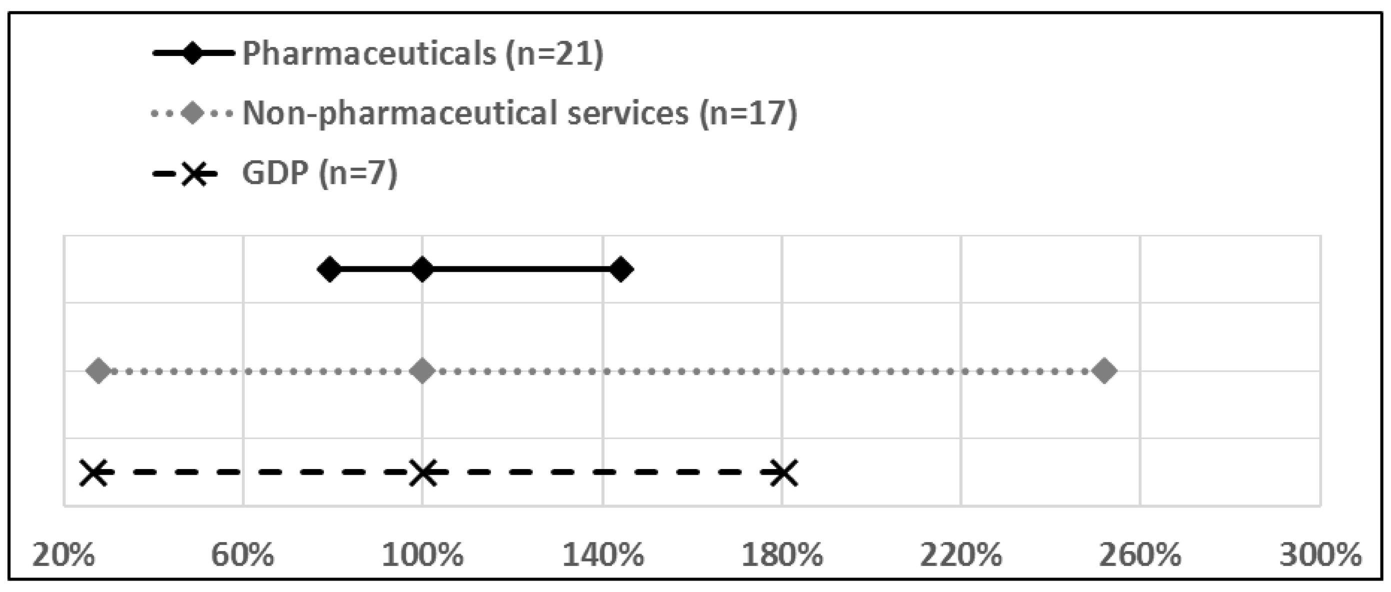


*Figure 1. Price-corridors for pharmaceuticals and non-pharmaceutical services compared to the variability in GDP per capita (100% represents the average of 7 countries)*

*Univariate regression analysis*

In the univariate linear regression analysis only one of the four EPR attributes had significant association with pharmaceutical list prices. Using lowest or the average of three lowest price from the basket translates to a 19.95% (p=0.029) decrease in list prices. GDP per capita and life expectancy were also found to be significant variables. A 1000 EUR GDP per capita increase is associated with 1.03% (p= 0.003), and one year increase in life expectancy is associated with 2.78% (p=0.012) increase in list prices, respectively. However, there was a strong correlation between economic status and life expectancy (0.7649).

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Population size was also found to be a significant country-specific control variable in the univariate analysis. We found that one million increase in inhabitants is associated with 0.40% (p=0.047) increase in list prices. Number of referenced countries, number of other countries referencing an individual country and rule of price revision had no significant association with pharmaceutical prices.

*Multivariate regression analysis*

According to the base case multivariate regression model the effect of GDP per capita and population remained significant. A 1000 EUR increase in GDP per capita associated with 1.1% (p<0.000) increase in list prices and one million increase in population size associated with 0.3% (p=0.001) price increase if all other variable included in the model remain fixed. Only one attribute of EPR, number of other countries referencing an individual country was statistically significant. Positive coefficient for the linear term (.1361, p= 0.012) was found and the quadratic term shows a slightly negative and significant trend (-.0056, p=0.003). This means that being referenced by more country increases list prices but in a decreasing extent until reaching a saturation point.

| Variable | Coefficient | Standard Error | P>\|t\| | 95% Confidence Interval | R^2 |
|---|---|---|---|---|---|
| **GDP per capita** | .0105 | .0022 | 0.000 | .0058 .0151 | 0.5007 |
| **Population size** | .0028 | .0007 | 0.001 | .0013 .0042 | |
| **Number of referenced countries** | .0125 | .0094 | 0.204 | -.0077 .0327 | |
| ***Squared value*** | -.0004 | .0003 | 0.154 | -.0010 .0002 | |
| **Number of other countries referencing an individual country** | .1361 | .0468 | 0.012 | .0356 .2365 | |
| ***Squared value*** | -.0056 | .0016 | 0.003 | -.0090 -.0023 | |
| **Rule of calculating reference price** | -.0561 | .0473 | 0.256 | -.1576 .0455 | |
| **Rule of price revision** | .0172 | .0390 | 0.667 | -.0665 .1008 | |

Table 2.Multivariate regression analysis including EPR attributes, GDP per capita and population size

## DISCUSSION

The European price corridor of pharmaceuticals is relatively narrow compared to the price corridor of non-pharmaceutical services or the variability of countries' economic status. Consequently, high-cost medicines are often not cost-effective and affordable in lower income countries. This result is in line with similar research conducted in the Middle East region [4]. Nonetheless the narrow price corridor may partially explain that spending on pharmaceuticals measured as a percentage of total healthcare spending is higher in CEE countries as they have lower income [6]. This effect may be facilitated by current practices of EPR in which countries use prices from other national markets without reflecting on their domestic economic situation or healthcare needs.

Moderate positive correlation (0.7161) between GDP per capita and number of countries referencing an individual country indicates that higher income countries are referenced more often than lower income countries. This supports the observation that CEE countries are necessitated to reference each other and higher income WE countries as well because manufacturers tend to launch their products initially in high income and strategically more important countries. Not referencing WE countries would limit their access to price information. Moderate negative correlation (-0.6807) between GDP per capita and rule of price setting indicates that lower income countries are more likely to mandate lowest price from the basket. This results in "race to the bottom" effect in pharmaceutical prices among CEE countries.

Although EPR is considered to be an effective cost containment instrument, this research found only limited evidence that supports the direct influence of EPR on pharmaceutical list prices. On the other hand, results show that population and GDP per capita are important and significant factors for setting pharmaceutical list prices in Europe.

The population effect may be contradictory to the hypothesis that larger countries have greater power to influence pharmaceutical prices. However, in Europe there has been a trend in the 90s, relatively large and less affluent postcommunist countries fell apart, whilst this trend was not visible in WE, what is more West- and East-Germany were reunited. In our sample almost all countries with large population size have higher income and all lower income countries had small population size, except Poland. The GDP effect on population size might explain why larger countries have higher pharmaceutical list prices. Large countries, however, may have more power to achieve greater confidential price discounts. Unfortunately we could not capture this aspect in our analysis.

The relatively minor impact of EPR on pharmaceutical prices can be explained by potential compensatory mechanisms of policymakers in individual countries and pharmaceutical companies to overcome negative consequences of EPR:

- Manufacturers tend to launch their new products in higher income and larger countries to set relatively high initial prices in these important markets. Therefore there is less room for EPR implementation in these higher income countries in the early period after market authorisation.
- Regulators in lower income countries usually mandate the lowest European price, and therefore lower GDP partially explains this aspect of EPR.
- Manufacturers often delay the product launch in those lower income countries with expectations of lowest pharmaceutical prices. Hence the price erosion effect of EPR is delayed and becomes limited in these countries due to careful design of launch sequence.
- Finally several European countries routinely apply confidential price discounts to improve patient access by alleviating affordability constraints in parallel with maintaining high list prices, so that other countries cannot free-ride on these confidential agreements through the EPR cascade.

The potential consequences of these compensatory mechanisms are that 1) several elements of EPR cannot be directly associated with narrow European price corridor, and 2) lower income countries usually have slightly lower pharmaceutical list prices.

Number of countries referencing an individual country still seems to be an important indirect factor of pharmaceutical list prices. However, this effect can be observed only until a certain number of countries, after which this effect is diminished.

### Conclusion

Our study indicates small range of price variation for pharmaceuticals in Europe. GDP seems to be still an important factor of pharmaceutical list prices. However, price variability according to GDP is not strong enough to sufficiently reflect on the actual economic situation and affordability of countries with lower income. Smaller number of countries referencing an individual country and mandating lowest price from the basket for price setting might have an effect in decreasing pharmaceutical prices, but this should be analysed in more detailed research focusing on these particular problems.

If current trend of price-convergence is strengthened, prices of pharmaceutical products may not be reflective to national market conditions anymore. Differential pharmaceutical pricing is vitally important to CEE countries with even more limited health care resources to improve patients access to new medicines and affordability of financing pharmaceuticals .

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