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July 2022

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Spillovers of Pharmaceutical Price Regulations: evidence from the AMNOG Reform in Germany

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July 15, 2022

Abstract

In years of growing pharmaceutical spending, the adoption of new health technologies faces several regulatory hurdles. Such policies are typically studied at the country level, even though there are explicit and implicit channels that link decisions made in different countries. This can be relevant in the EU, where external reference pricing is widely adopted. This work exploits the IMS pricing database of cancer drugs approved by the European Medicine Agency between 2007 and 2017 to assess the impact of a pharmaceutical pricing regulation change that occurred in Germany in 2011 (the AMNOG bill) on foreign pharmaceutical prices. We show that the impact on foreign prices depends on whether the foreign country adopts external reference pricing policies and whether it includes Germany in its basket of reference countries and, symmetrically, if it enters Germany's reference set. In particular, our diff-in-diff approach shows that AMNOG led to a price reduction for products launched in countries that refer to Germany (indirect spillover effect), whereas products launched in countries referenced by Germany experienced a 5.48% price increase (strategic spillover effect).

Keywords: AMNOG, pharmaceutical regulation, External Reference Pricing, difference-in-difference, spillover effect. **JEL codes:** I18, O38, C78.

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1 Introduction

In recent years, global spending on medicines has been constantly increasing worldwide (GCO, 2020). Numerous efforts have been put in place to contain the disproportionate expansion of costs, especially in the European pharmaceutical market (Vogler et al., 2011). One of the main paths followed by European Regulators is represented by the reliance on external reference pricing (ERP) (Rémuzat et al., 2015; Espin et al., 2014; Kanavos et al., 2020), especially in countries with expanding healthcare coverage (Holtorf et al., 2019). As defined by the World Health Organization (WHO, 2013), the practice of ERP consists in using the price of new medicines in one or several countries in order to derive a reference price. This benchmark is then used for setting or negotiating the price of the new products, so that the pharmaceutical market in the EU can be considered as the result of the interplay of different national pharmaceutical regulations. Although quite heterogeneous[1], ERP regulations have the common aim of ensuring that countries do not overpay for new medicines with respect to their neighbours.

With few exceptions (Stargardt and Schreyögg, 2006; Richter, 2008), policies regarding pharmaceutical regulations are studied at the country level (Brekke et al., 2009; Kaiser et al., 2014; Windmeijer et al., 2006), even though the widespread presence of ERP schemes explicitly link decisions made in different countries. Our objective is to analyse the impact of a new health technology assessment (HTA) in a European country on pharmaceutical prices in other countries in Europe. With this purpose, we exploit the HTA procedure introduced in 2011 in Germany, the Act to Reorganize the Pharmaceuticals Market (AMNOG)[2]. Before the reform, manufacturers were largely free to set prices of new innovative drugs, whereas the bill imposed negotiations between manufacturers and the regulatory bodies based on: *i)* the added therapeutic value of the drug with respect to the best alternative available; *ii)* the EU price level of the product. We expect the domestic price variations caused by the reform to propagate to other countries. The main channel is the ERP criterion adopted by different EU countries, provided that their specific ERP reference set includes the country that introduced the reform—in our case, Germany. We define this effect of the reform

[1] See Table A2 for an update overview of all ERP methods in use.

[2] Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) bill (in German): https://dserver.bundestag.de/btd/17/024/1702413.pdf.

as indirect (hereafter, *indirect spillover*) since it is affecting other countries than the one introducing the reform and we expect it to be of the same sign of the domestic price variation. Evidence from the AMNOG legislation introduced in Germany in 2011 points towards a negative domestic effect on anticancer prices[3]; the present work shows that the domestic price variation due to AMNOG negotiation process has propagated on prices set in foreign countries that include Germany in their own ERP reference set.

The introduction of the ERP policy in the AMNOG legislation allows us to analyse also the effect of this kind of policy on the price set in foreign countries. Manufacturers might put more effort in the attempt of negotiating a higher price in countries that are included in the ERP reference set of "key" countries (e.g. with a large market share, such as Germany), in order to set a higher price even in the "key" countries. In the German case, we expect that the ERP criterion embedded in the AMNOG legislation might have led to this manufacturers' strategic behavior in foreign countries that are in the German ERP reference set. We set a Nash bargaining framework in which the Home country introduces a new pharmaceutical regulation with an ERP criterion and includes a Foreign country in its ERP reference set. The results are suggestive of a strictly positive impact of the domestic reform on foreign prices resulting from the Nash bargain between the manufacturer and the Foreign country regulator. We call this positive impact of the reform on prices set in another country as *strategic spillover* and we provide evidence that, on average, prices that can be considered for the ERP criterion in the AMNOG process are, on average, higher in those countries that belong to the German ERP reference set.

For our empirical analysis we use the IMS pricing database, which includes a panel of quarterly prices for anticancer drugs approved by EMA that were launched in 25 OECD countries from 2007 to 2017. To detect the impact of the AMNOG reform on foreign prices (both the indirect and the strategic spillover), we employed a difference-in-differences method.

The present work proceeds as follows: Section 2 reviews in detail the reform that occurred in Germany in 2011 and outlines the existing literature; Section 3 proposes a simple theoretical framework; Section 4 sets out the identification strategy that has been used in the analysis; Section 5 provides a brief overview of the data employed and

[3] Lauenroth et al. (2020), as well as our own forthcoming work on the AMNOG causal domestic effect on German anticancer prices.

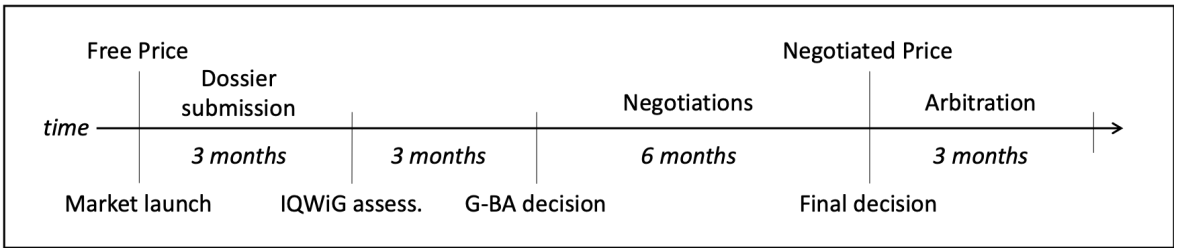
Section 6 presents the results. Finally, Section 7 summarizes the findings and concludes the work.

2 Background

2.1 The AMNOG reform in Germany

Before the AMNOG bill, which came into force on January 1, 2011 there was no "fourth hurdle" for new products in Germany: pharmaceutical manufacturers could freely set their price once the European Medicines Agency (EMA) granted market authorization. The AMNOG act, instead, prescribes that manufacturers that obtain EMA approval are free to set prices, as before, for a maximum of twelve months. At the end of this period, pharmaceuticals that do not offer additional therapeutic benefits, as assessed by the Joint Committee (G-BA)[4] in accordance with the Institute for Quality and Efficiency in Health Care (IQWiG), will be directly included in Germany's reference pricing system, as prior to the reform. All medicines that demonstrate a clinical added value will be subject to price negotiations between the Federal Association of Sickness Funds (SHI) and the manufacturer, in consultation with the Association of Private Health Insurance Companies (Ognyanova et al., 2011). The negotiating parts, considering the added value of the drug, have to converge to a final price before 12 months have passed since the launch date. Eventually, the agreed-upon price is adopted in place of the price set by the manufacturer.[5] All steps are summarized in Figure 1.

Figure 1: AMNOG process medicines with added therapeutic value with respect the appropriate comparator. Adapted from Ruof et al. Ruof et al. (2014)



[4]The G-BA is the key legal institution of the self-administered German health care system.

[5]In case no agreement is reached after the twelve months, an Arbitration Board examines the case and takes his final decision up to three months. The Arbitration Board is composed of one impartial chairman, two impartial members and two representatives of each negotiation party. Until 2015 only 15% of all negotiation ended up to the arbitration stage (Ludwig and Dintsios, 2016).

During the negotiation process, stakeholders and decision-making bodies can take into account prices paid in other European countries as a supportive criterion (external reference pricing). The reference is the price level of the product calculated as the cross-country average of ex-factory prices per defined daily dose, weighted by each country's purchasing power parity and population size (Lauenroth and Stargardt, 2017). Countries whose prices are referred to are Belgium, Denmark, Finland, France, UK, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Spain, and the Czech Republic.[6]

2.2 Existing Literature

Up to May 2018, the AMNOG reform led to the assessment of 307 new medicines by the entitled HTA bodies (the G-BA and the IQWiG). A total of 52 medicines were eventually assessed as innovative with respect to the available comparators and, thus, subject to the price negotiation process prescribed by the AMNOG legislation (Wenzl et al., 2018). Lauenroth et al. (2020) report a difference of 24.5% between launch prices and negotiated prices of innovative products in Germany, mostly due to a closer alignment between the added benefit of the drug and its price. Moreover, our own calculation (unpublished) confirmed that the overall causal effect of AMNOG on anticancer drugs is a 15.1% price reduction for the period 2011-2017, on average. In theory, this price reduction may be due to the negotiation process between the regulator and the manufacturer, or to the adoption of the ERP. However, Paris and Belloni (2013) claim that ERP plays a minor role in Germany, while European Commission (2015) suggests that the ERP criterion is not even used in practice. Lauenroth and Stargardt (2017) seem to confirm the former view: they find that the EU price level is correlated with the price premium of the innovative drug that is under the scope of AMNOG; although significant, the effect found Lauenroth and Stargardt is rather small.

Strategic interactions among countries in pharmaceutical price regulations have been already documented (Kyle et al., 2017). It is also widely accepted that the presence of ERP schemes leads to a downward price convergence over time, although the empirical evidence is limited (Leopold et al., 2012; Csanádi et al., 2018; Kaló et al.,

[6]Countries included in the list: *i)* must be part of the European Economic Area (EEA); *ii)* must together account for at least 80% of the population of the EEA (without Germany); and *iii)* must be comparable to Germany in terms of their economic performance. (Ludwig and Dintsios, 2016).

2015) and sometimes weak, as suggested by literature surveys (Espin et al., 2014; Kanavos et al., 2017). Because of the adoption of the ERP practice in other countries, the domestic price variation due to the AMNOG reform in Germany might have triggered a cascade effect on foreign prices: this is predicted by different simulation exercises (Toumi et al., 2014; Vogler et al., 2020; Merkur and Mossialos, 2007). Stargardt and Schreyögg (2006) develop a simulation model to assess the effect of a price reduction of €1 in Germany, both in terms of direct impact (the effect directly imputable to the inclusion of Germany in the reference basket of other countries) and in terms of indirect impact (the effect due to the inclusion in the reference basket of countries that are referencing to Germany). The sum of these two effects ranges from €-0.15 in Austria to €-0.36 in Italy. This corresponds to our definition of indirect spillover effect and, although intuitive in the context of ERP, remains empirically unexplored.[7]

From a theoretical perspective, Garcia Mariñoso et al. (2011) consider a simple home-foreign country model and show that the introduction of an ERP scheme in the home country can increase foreign prices. This is close to our definition of strategic effect. Geng and Saggi (2017) compare ERP to direct price control in a two countries (home-foreign) model. They conclude that home's ERP policy generates a negative price spillover for foreign consumers by design, which is confirmed by our findings. Birg (2016) models different ERP schemes in a three-countries framework and concludes that, if the market size of the country adopting an external reference pricing scheme is sufficiently large, the manufacturer does not sell to the other countries. Houy and Jelovac (2015) investigate optimal timing decisions in a dynamic setting in the context of a price cap-type of ERP. They show that countries where the drug is sold are those with largest willingness to pay, and that there exists an optimal price vector for which, if the drug is sold, it is sold from the first period.

[7]Although in this paper we only explore the price dimension of the ERP channel, the presence of an ERP scheme is also expected to have a time dimension, as it is often related to market launch delays in low-income countries (Maini and Pammolli, 2020; Kyle, 2007; Lanjouw, 2005) or in countries with more stringent regulations (Danzon et al., 2005; Heuer et al., 2007). This occurs because of the attempt by manufacturers to avoid the propagation of lower prices in richer countries due to cross-referencing or, in the latter case, to signal against tighter price regulation (Lakdawalla, 2018).

3 Theoretical Framework and Hypotheses

Let us define as Home country (H) the country which introduces price negotiation, and as Foreign country (F) the country potentially subject to spillovers. We define two types of spillovers. *Indirect spillovers* may occur when: *i*) product i is launched earlier in Home than in Foreign country; *ii*) Home country belongs to Foreign ERP reference set; *iii*) product i falls into the ERP scope in the Foreign country. *Strategic spillovers*, instead, occur when: *i*) product i is launched in the Foreign country before it is launched in the Home country[8]; *ii*) Foreign country enters Home country's ERP reference set; *iii*) product i falls into the ERP scope in the Home country. In this situation, the manufacturer might be willing to put more effort in raising the price of product i in the Foreign country, knowing that the resulting price will influence even the price in the Home country.

Indirect Effect The theoretical justification of the indirect effect is intuitive: if the price of product i in the Foreign country is function of the price of product i in the Home country through a certain ERP rule, a price variation in Home country would ultimately translate into a price variation of the same sign in Foreign country too. We assume that the new regulation enters in force in Home country at time t. We define p_{it}^H as the price adopted for product i at time t under the new regulation, and $\tilde{p}_{it}^H$ the price that would have been set in the absence of the reform. We call Δ_t the price variation for product i in the Home country that is due to the new regulation, so that $\Delta_t = p_{it}^H - \tilde{p}_{it}^H$; the price of product i at time t in H would be $p_{it}^H = \tilde{p}_{it}^H + \Delta_t$. At time $t+1$, Foreign country launches the same product i, which falls under its ERP scope. Let $\mathcal{R}(p_{it}^H)$ be the specific ERP rule adopted in the Foreign country, and let it be a monotonic function of p_{it}^H. Under the new regulation adopted by the Home country at time t, the price of product i in the Foreign country in $t+1$ is the following:

$$p_{i,t+1}^{F(H)} = \mathcal{R}(p_{i,t}^H) = \mathcal{R}(\tilde{p}_{i,t}^H + \Delta_t)$$

[8] Or, at least, before the effect of the reform takes place. This caveat is particularly relevant in the case of AMNOG legislation, where the effect of the negotiation process are visible only after one year from the product launch in Germany. This is outlined in detail in Section 4

where the superscript $F(H)$ means that Foreign country refers to Home country in its ERP reference set. The indirect effect δ is defined as the effect of the price variation due to the reform on the price in the Foreign country:

$$\delta_{i,t+1} = \frac{\partial \mathcal{R}(\tilde{p}^H_{i,t} + \Delta_t)}{\partial \Delta_t} \Delta_t$$

The impact δ_t on the price in the Foreign country has the same sign of the Home country price variations Δ_t, since $\partial \mathcal{R}(\tilde{p}^H_{i,t} + \Delta_t)/\partial \Delta_t$ is positive. Since other studies (Lauenroth et al., 2020), as well as with our own calculations, point to a negative domestic price variation due to the AMNOG reform (so to a negative Δ_{AMNOG}), we expect a negative indirect spillover effect.

Strategic Effect As for the strategic effect, we propose the following theoretical justification, based on the Generalized Nash Bargaining[9] framework. To the Home-Foreign country setup we add the Manufacturer (M), which does not belong to any country. The Manufacturer develops a new pharmaceutical product i, which is granted safety and efficacy permits by a supranational regulator. Patent protection is assumed to last forever. Let m_i and $1 - m_i$ be the inelastic demands for product i in Home and Foreign country, respectively, which have a marginal benefit from consumption of product i equal to w_{iH} and w_{iF}, with $w_{iH} > w_{iF}$. The Manufacturer maximizes the profit made by selling product i, $\Pi_i = \pi^H_i(p_{iH}, m_i) + \pi^F_i(p_{iF}, m_i)$, where p_{iH} and p_{iF} are the prices resulted from the negotiation process. Profits π^H_i and π^F_i are the profits made in Home and Foreign country, which, in turn, maximize their surplus $S_{ci}(w_{ci}, p_{ci}, m_i)$, where $c = \{H, F\}$. In case the product is not launched, the surplus is equal to zero. Subscripts for product i are dropped hereafter for simplicity.

One of the requirement for the presence of the strategic effect is that product i is launched in the Foreign before it is launched in the Home country: for this reason, the game is divided in two steps in which the Manufacturer first negotiates with Foreign

[9]The price negotiation for product i between country $c = \{H, F\}$ and the manufacturer M boils down to the maximization problem $\max_{\{p_{ci}\}} [U_c(p_{ci}) - d_c(.)]^{\gamma} [U_M(p_{ci}) - d_M(.)]^{1-\gamma}$, where U_c and U_M are the payoffs of the two agents in case they reach an agreement and d_c and d_M are the so-called "disagreement payoffs" (DP), the payoffs that agents obtain in case the negotiation fails (with $U_c \geq d_c$ and $U_M \geq d_M$). In our case, U_c is the surplus of country c while U_M is the profit of the firm. Finally, γ (with $0 < \gamma < 1$) is the relative bargaining power of the first agent. The Equation above represents the product of the two agents' utility-DP difference, which is called *Nash product* (NP). The price that maximizes the NP would be the price that the agents are willing to accept. See Muthoo (1999).

country the price p_F ($M\,vs\,F$ negotiation), and then it negotiates the price p_H with the Home country ($M\ vs\ H$ negotiation). Therefore, we proceed by backward induction, first looking at the price resulting from the negotiation between the Manufacturer and the Home country and then at the negotiation between the Manufacturer and the Foreign country. This is done both in the scenario in which Home country does not adopt ERP (no ERP scenario) and in the scenario where it does and it includes Foreign country in its reference set (ERP scenario).

In the $M vs H$ negotiation of the no ERP scenario, in case of success of the Nash bargaining, the payoff of the Manufacturer is $\Pi = \left(\pi^H + \pi^F\right)^{1-\gamma} = [\tilde{p}_H m + \tilde{p}_F(1-m)]^{1-\gamma}$ while the payoff of country H is equal to $S_H = [(w_H - \tilde{p}_H)m]^{\gamma}$, where γ and $1-\gamma$ are the relative bargaining powers of the two agents, while $\tilde{p}_H$ and $\tilde{p}_F$ are the prices applied separately in the two markets. Symmetrically, the payoffs in case of failure—the so-called disagreement payoffs—are $d_M = (\pi_M^F)^{1-\gamma} = [\tilde{p}_F(1-m)]^{1-\gamma}$ and $d_H = 0$. In fact, the Manufacturer that is not able to converge to an agreement to sell in Home country can still make a profit in Foreign country, while, in case of failure, we assumed that the Home country would obtain a surplus equal to zero. The price that results from the application of the above payoffs to the Nash bargaining framework is $\tilde{p}_H^* = w_H(1-\gamma)$. As the intuition suggests, under the no ERP scenario the optimal price $\tilde{p}_H^*$ only depends on the marginal benefit of Home country and on the relative bargaining power of the two agents. The $M\,vs\,F$ negotiation with no ERP proceeds in an analogous way, but in this case the relative bargaining power is defined as μ and the Manufacturer, in case of failure, would still be able to sell product i in Home country. The resulting optimal price is $\tilde{p}_F^* = w_F(1-\mu)$.

Under the ERP scenario, Home country relies on ERP and refers to Foreign country with a price cap rule—that is, we assume that the price adopted in the Home country, p_H, is the result of a linear combination between the price that would have been set without ERP, $\tilde{p}_H$, and the price of the product in the country that enters Home's reference set (in this case, just the Foreign country). The linear combination is shown below.

$$p_H = (1-\alpha)\tilde{p}_H + \alpha p_F \tag{1}$$

If $\alpha = 0$ there is no ERP consideration and the price would be equal to the price in

the absence of the ERP, so $p_H(\alpha = 0) = \tilde{p}_H$. In case $\alpha = 1$ the ERP criterion would be the only considered by Home regulator in setting i's price: it simply "borrows" the price set by Foreign regulator once product i is adopted, so that $p_H(\alpha = 1) = p_F$. In other words, α is the weight that is given to p_F in setting the price that is eventually adopted in Home country, and this is the reason why α can be thought of as a sort of "ERP intensity". Therefore, in our ERP setup, the *M vs H* negotiation boils down to the linear combination between what can be thought of as the counterfactual price, $\tilde{p}_H$, and the price resulted from the *M vs F* negotiation in case the Home country adopts ERP. Therefore $p_H = (1-\alpha)\tilde{p}^*_H + \alpha p_F$ can be rewritten as $p_H = w_H(1-\alpha)(1-\gamma) + \alpha p_F$.

As for the *M vs. F* negotiation under the ERP scenario, in case of a successful negotiation the profit of the Manufacturer is equal to the sum of the profits made in both countries, incorporating the new price in Home country as in Equation 1, thus $\Pi = [[(1-\alpha)\tilde{p}^*_H + \alpha p_F]m + p_F(1-m)]^{1-\mu}$, which can be rewritten as $\Pi = [[w_H(1-\alpha)(1-\gamma) + \alpha p_F]m + p_F(1-m)]^{1-\mu}$. The payoff obtained by Foreign country remains equal to $S_F = [(w_F - p_F)(1-m)]^{\mu}$. On the other hand, in case of failure, the Manufacturer would still be able to sell the product in the Home market, but without the price negotiated with the Foreign regulator there would not be any price cap. Therefore, the disagreement payoff would be equal to $d_M = \tilde{p}^*_H m = w_H m(1-\gamma)$. The disagreement payoff of F is still equal to zero.

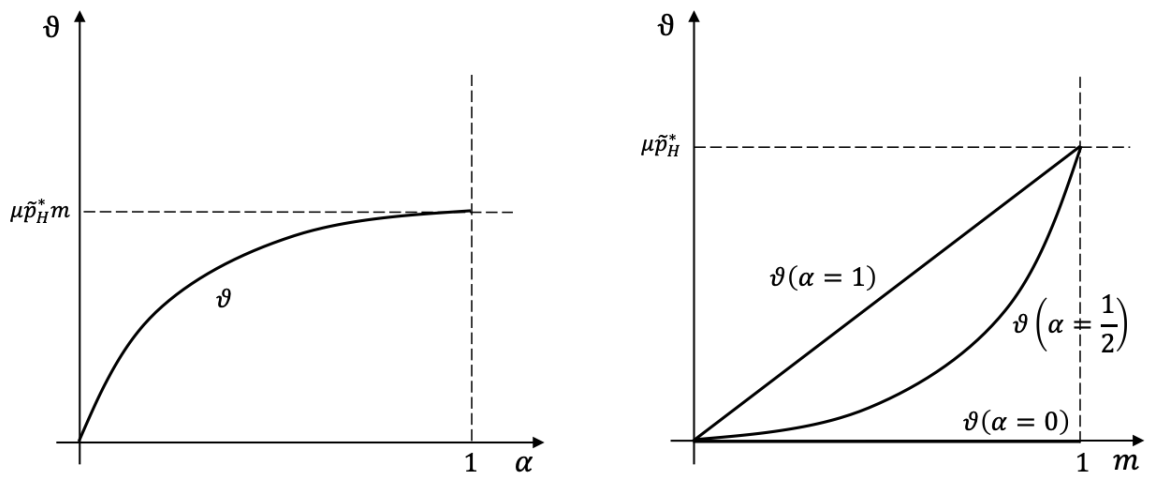
The first order conditions lead to the optimal price equal to $p^*_F = w_F(1-\mu) + \frac{\mu\alpha w_H(1-\gamma)m}{\alpha m+1-m}$. Comparing it with the price in the Foreign country under the no ERP scenario, we obtain the strategic effect as their difference:

$$\vartheta = p^*_F - \tilde{p}_F = \frac{\mu\alpha w_H(1-\gamma)m}{\alpha m+1-m} \tag{2}$$

Proposition 1 *The introduction of the ERP criterion in the Home country always raises prices for the Foreign country, for any value of α, m, μ and γ, with respect to the no ERP scenario. As ERP tightens in Home country, the strategic effect ϑ increases, since $\frac{\partial\vartheta(\alpha,m)}{\partial\alpha} > 0$ and $\frac{\partial^2\vartheta(\alpha,m)}{\partial^2\alpha} < 0$. As the market share of Home market increases, the Manufacturer has a stronger incentive to increase the price in the Foreign country to affect the price in the Home market, since $\frac{\partial\vartheta(\alpha,m)}{\partial m} > 0$ and $\frac{\partial^2\vartheta(\alpha,m)}{\partial^2 m} > 0$.*

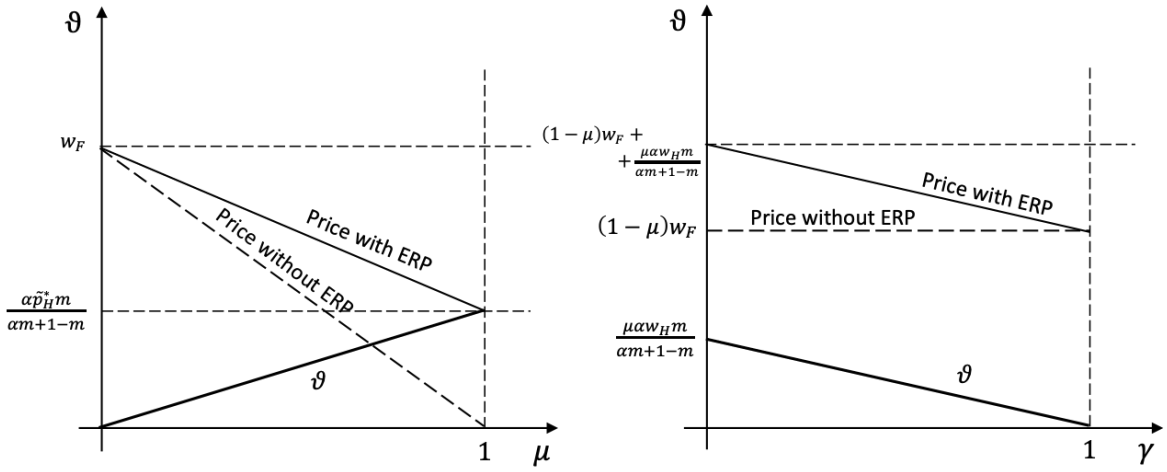
The graphical representation of the Proposition above is shown in Figure 2. Finally, both μ and γ are inversely and linearly correlated with p^*_F: as the bargaining power of

Figure 2: Strategic effect as a function of α and m



country F (or country H) increases, we expect that the optimal price in F decreases (and so does in country H, since the same price is adopted because of ERP). In fact, we have that $\frac{\partial p_F^*}{\partial \mu} < 0$ and $\frac{\partial p_F^*}{\partial \gamma} < 0$, as it can be seen in Figure 3.

Figure 3: Optimal price in F as a function of μ and γ



The simple setup proposed for the strategic effect seems to suggest that, regardless of the magnitude and the sign of the Home price variation and the nature of the Home country's ERP process that is implemented, the price that results from the negotiation process will always increase in Foreign country in response to the introduction of ERP

by the Home regulator. The magnitude of the increase is directly associated to the "intensity" of ERP and to Home market share (and inversely correlated to the Foreign market share) and inversely correlated to each country's bargaining power relative to Manufacturer's. In the case of AMNOG legislation in Germany, the introduction of the ERP criterion should have changed the parameter α from zero to a value greater than zero, so that we should observe a positive impact on foreign products as a response.

4 Empirical Method

In the previous Sections, we outlined the mechanisms that we expect to be at play through the ERP channel when a new price regulation is introduced. In the following, we provide empirical evidence for these effects. We exploit the introduction of price negotiation in Germany in 2011, with the AMNOG bill, in order to determine whether the impact of this specific regulation has propagated on foreign countries. Other studies are suggestive for a negative domestic price variation—in our notation, $\Delta_{AMNOG} < 0$. Thus, we expect the indirect effect δ_{AMNOG} to be negative for all countries that included Germany in their ERP reference basket. Also, we expect the strategic effect ϑ_{AMNOG} to be always positive for those countries that, after 2011, were included in the German ERP reference set.

4.1 Indirect Effect

In order to analyse the effect of the German reform on prices set in other countries, we adopt a Difference-in-differences (DiD) method and we estimate the following regression:

$$y_{ict} = \beta_0 + \beta_1 T_{ic} + \beta_2 POST_{it} + \delta_{AMNOG}(T_{ic} \times POST_{it}) + \beta_2 \mathbf{X}_{ct} + \beta_3 PREV_{ict} + \theta_i + \delta_t + \gamma_c + \varepsilon_{ict} \tag{3}$$

where the dependent variable y_{ict} is the natural logarithm of the price of product i for country c at time t. The dummy T_{ic} identifies as treated group ($T_{ic} = 1$) all observations referring to countries that apply an ERP policy, that have Germany in their ERP reference set, and that adopt the ERP policy for product i. The dummy $POST_{it}$ is

equal to 1 if product i at time t has a negotiated price in Germany, and 0 otherwise. This means that $POST_{it}$ is equal to 0 for all observations antecedent to 2012,[10] as well as for those products launched in Germany before 2011 (for which the price has never been negotiated in Germany). Our interest lies in the coefficient δ_{AMNOG} of the interaction term. $PREV_{cti}$ is the prevalence, in country c at time t, for disease(s) treated by product i. $\mathbf{X}_{ct}$ is a vector of country, time-dependent characteristics driving pharmaceutical prices, such as GDP. We include a product fixed effect θ_i to account for different levels of products' effectiveness, and to take into account for the important differences in the price per mg among different products. Also, we include a quarter fixed effect δ_t to control for any pharmaceutical price trends.

4.2 Strategic Effect

We now analyse a foreign product j that is launched before the same product j has completed the negotiation process in Germany. Recall that we expect the price of the foreign product j to have increased with respect to what would have been set instead, in response to the—newly introduced—ERP criterion of the German price setting process, which is active one year after j's launch. For the strategic spillover analysis we consider products' observations occurred between t_{0j} and $s_j + 4$, where t_{0j} is the launch date of product j in the foreign country (with $t_{0j} < s_j + 4$).

The framework that is employed is a Difference-in-difference in which we compare the price of potentially affected products (as we have defined them above) of treated units with control units, and the difference that is obtained is compared between pre and post reform. Equation 3 shows the empirical model that identifies the strategic spillover effect.

$$\begin{aligned} y_{jct}(t_{0j} < t_j < s_j + 4) =& \beta_0 + \beta_1 T_c + \beta_2 POST_{jt} + \\ &+ \vartheta_{AMNOG}(T_c \times POST_{jt}) + \beta_3 \mathbf{X}_{ct} + \theta_j + \delta_t + \gamma_c + \varepsilon_{jct} \end{aligned} \tag{4}$$

Potentially affected products' observations are defined by the condition $t_{0j} < t_j < s_j + 4$. Again, the dependent variable y_{jct} is the natural logarithm of the price of product j for country c at time t, and time is in quarters of a year. $\mathbf{X}_{ct}$ is the vector of country

[10] The AMNOG bill came into force on January 1, 2011, thus until January 1, 2012, all pharmaceutical prices in Germany were still unregulated.

characteristics driving pharmaceutical price dynamics. We also include product, year and country fixed effect. Our interest lies in the coefficient ϑ_{AMNOG} of the double interaction term, where $POST_{jt} = 1$ if product j has been launched in Germany after 2011 ($s_j >$ 2011 Q1) and $POST_{jt} = 0$ otherwise. The dummy T_c refers to whether country c is in the ERP basket of Germany or it belongs to the control group.

Control units for the strategic spillover effect must be chosen among those countries that are not in the reference basket of Germany. Among our sample, Hungary, Norway, Poland, Slovakia, Switzerland and Turkey are the only countries not included by Germany in its ERP basket for which we have pre- and post-treatment observations. Among those, Slovakia has no product that satisfies the requirement of being subject to strategic spillover effect, while Poland and Turkey have just one product each in the pre-treatment period, so they are as well ignored. In the analysis, we are left with Hungary, Norway and Switzerland in our pool of control units (see Table 3).

5 Data

The empirical analysis is conducted exploiting the Pricing Insights IMS database. IMS price data are particularly suitable for price comparisons among a large number of countries, and they have been already used in other studies because of their completeness (Pertile et al., 2018). Data on quarterly prices and information on the date of launch were retrieved for 74 non-generic antineoplastic (anticancer) drugs, authorised by EMA from 2007 to 2017.[11] Information are retrieved for the 25 countries which, in 2007, were members of the OECD. Anticancer products were chosen as they have driven the increase in pharmaceutical expenditure worldwide (Mariotto et al., 2011; Hofmarcher et al., 2020). All prices are converted in Euro using the quarterly exchange rate reported in the Pricing Insights IMS database. Also, prices have been recalculated to refer to a milligram (mg) of active substance. This choice is intended to make products, which might be sold with different pack sizes or different strengths, more comparable within and across countries. Moreover, when different prices are

[11] During this time span EMA authorized 108 antineoplastic drugs, but 34 of these had to be excluded: 6 do not treat cancer, 3 do not have prevalence data, 2 are hybrid drugs, 12 were not on patent, 2 were very recent and they are not in the price data set and 9 were introduced before the period covered. The complete list and the descriptive statistics of the remaining 74 products are provided in the Appendix, while Table 1 below shows the number of products available by country.

Table 1: Number of products available and date of the first observation, by country.

Country	*Num. prod.*	*First obs.*	*Country*	*Num. prod.*	*First obs.*
Austria	64	Q1 2007	Korea	22	Q1 2011
Belgium	45	Q1 2007	Luxembourg	1	Q3 2010
Czech Rep.	27	Q2 2011	Netherlands	31	Q2 2007
Denmark	60	Q3 2007	Norway	58	Q1 2007
Finland	43	Q1 2007	Poland	12	Q2 2007
France	51	Q1 2007	Slovak Rep.	20	Q2 2007
Germany	64	Q1 2007	Spain	50	Q1 2007
Greece	41	Q2 2007	Sweden	48	Q1 2007
Hungary	27	Q2 2007	Switzerland	44	Q2 2007
Ireland	51	Q3 2007	Turkey	17	Q3 2010
Italy	47	Q1 2007	UK	63	Q1 2007
Japan	33	Q1 2011	USA	49	Q4 2007

available for the same product at the same time within one country, the lowest price per mg is considered, because is deemed as the one relevant for the consumers. Most often, the price per mg refers to the price to the hospital (85.3%); when mandatory rebates are in force, the price refers to the manufacturer price less mandatory rebates price (13.5%); when the information is not available, the price refers either to the price to pharmacies or to the retail price (1.2%).

Data for prevalence are extracted from the Global Burden of Diseases (GBD) 2015 database Vos et al. (2016). Specifically, we referred to EMA therapeutic indications of the drug and matched them with the associated prevalence as indicated in the GBD database.[12] When more than one indication is expressed by EMA, we refer to the sum of all diseases' prevalence. Moreover, data on prevalence are available at 5 years intervals, therefore prevalence is assumed to remain constant within that time interval. Finally, data for GDP per capita are gathered from the World Bank Indicators and converted in Euro with the exchange rate in the Pricing Insights IMS database for consistency. The explanatory variables that we employed are those potentially relevant for the price negotiation dynamic and are summarized in Table 2. Similar to other empirical studies Leopold et al. (2012); Pertile et al. (2018); Kyle and Qian (2014); Cabrales and Jiménez-Martín (2013), we included GDP per capita to account for how much the national payer is willing to pay the manufacturer. We expect that

[12]We relied on the highest level of detail, that is level 3, of all diseases, as captured by the GBD database.

Table 2: Variables employed in the analysis.

Variable	*Type*	*Definition*	*Source*
Ln Price	cont.	natural logarithm of quarterly price per mg	Pricing Insights IMS database
Ln prev	cont.	Natural logarithm of the prevalence of diseases treated by product i in country c.	GBD 2015 database
Ln GDP pc	cont.	Natural logarithm of GDP per capita.	World Bank Indicator
Delay	cont.	Delay from first worldwide launch of product i in quarters.	Pricing Insights IMS database

higher per capita income would lead to higher prices, consistently with a lower price elasticity associated with higher income levels Cabrales and Jiménez-Martín (2013). We also included market size as a regressor because it can capture the incentive to negotiate higher prices by the manufacturer Kyle and Qian (2014); Puig-Junoy and López-Valcárcel (2014). Differently from Puig-Junoy and López-Valcárcel Puig-Junoy and López-Valcárcel (2014), however, who measured market size as the defined daily doses sold by competitors the previous year, we constructed market size using prevalence as a proxy, as in Pertile et al. Pertile et al. (2018). Finally, the variable *delay* measures the lag in the domestic launch with respect to the launch of the product worldwide. That could either capture the emergence of new molecules that could drive the price of the existing product down, or the cascade effect of ERP on the domestic launch price, or both.

A distinction between countries *referencing to* Germany and those *referenced by* Germany is provided in Table 3.

Table 3: Countries in the sample that are *referencing to* and that are *referenced by* Germany.

Country	*Ref.*	*Ref'd.*	*Country*	*Ref.*	*Ref'd.*	*Country*	*Ref.*	*Ref'd.*
Austria	✓	✓	Ireland	✓	✓	Portugal		✓
Belgium	✓	✓	Italy	‡	✓	Slovak Rep.	✓	✓
Czech Rep.		✓	Japan			Spain	✓	✓
Denmark	†	✓	Korea			Sweden		✓
Finland	✓	✓	Luxembourg			Switzerland	✓	
France	✓	✓	Netherlands	✓	✓	Turkey		
Greece	✓	§	Norway	✓		UK		✓
Hungary	✓		Poland	✓		USA		

† refers to Germany since ERP introduction in 2009; ‡ basket composition not clear;
§ temporarily excluded from German basket.

In our dataset, only Sweden, the UK and the US satisfy this condition, since their pricing methods are is not based on EU prices[13]. Thus, it is reasonable to assume that there should not be any spillover from the AMNOG reform, making them suitable candidates as controls.

6 Results

Robust standard error estimation clustered at the product level was used. The statistical analysis is performed with Stata/SE 13.

6.1 Indirect Effect

Table 4 shows the results for the indirect spillover. It can be observed that the coefficient of the interaction term is not significant under any model that is tested. One possible reason is that treated products launched before the reform are observed for a longer time span and thus are more subject to cross-country price variations with respect to treated products launched after the reform. Most importantly, treated products launched before the reform are more subject to cross-country price variations than control countries. In fact, since we have chosen control units that do not adopt ERP, we should expect that the price of their products to be less affected by price variations from other countries over time. In general, those cross-country price variations that occur over time might have nothing to do with the AMNOG reform, and thus they might bias our result leading to an underestimation of our coefficient of interest. Specifically, the average price considering all product observations occurred 12 months

[13]Sweden adopts a form of value-based pricing in which the pharmaceutical company submits an application that includes documentation regarding the clinical effect and the cost-effectiveness of the product. The final approval is granted by regulatory bodies based on the assessment of certain principles of value. Specifically, *i)* the human value principle, ii) the need and solidarity principle, and iii) the cost–effectiveness principle (Pontén et al., 2017). As for the UK, the Pharmaceutical Price Regulation Scheme (PPRS) regulates the profit that companies can achieve on sales to the National Health System (NHS), and the National Institute for Health and Clinical Excellence (NICE) is entitled to provide national guidance to the NHS through recommendations on the cost–effectiveness of new medicines (Kullman, 2010). The US, instead, has been under a free pricing regime, although there has been a debate over the possible inclusion of ERP considerations. For instance, under the Trump administration, the House of Representatives passed the Lower Drug Costs Now Act (2019), which included the provision of a "maximum fair price" based on the lowest list price across a basket of countries for the most expensive drugs in Medicare Part D. In recent days, President Biden is questioning whether to adopt or strike the previous ruling.

after German launch will be excessively low for treated countries, and thus the first difference pre reform for treated countries would offset the first difference post reform for treated countries.

Table 4: Indirect spillover effect.

	Fixed Effect DiD Model					
Dep. Var.: Ln price	(1)		(2)		(3)	
T=1 × Post=1	0.00176	(0.0473)	-0.0520	(0.0312)	-0.0282	(0.0313)
T=1	-0.00328	(0.0227)	0.448***	(0.143)	-0.233*	(0.130)
Post=1	-0.0742*	(0.0387)	0.0516**	(0.0211)	0.0303	(0.0211)
Ln prev					0.0240	(0.0307)
Ln GDP pc					0.533***	(0.0538)
Launch delay					0.000409	(0.00220)
Constant	1.102***	(0.0177)	0.755***	(0.140)	-4.540***	(0.733)
Product FE	No		Yes		Yes	
Time FE	No		Yes		Yes	
Observations	10143		10143		10143	
R2_within	0.00555		0.471		0.488	
R2_between	0.0152		0.0802		0.0935	
R2_overall	0.00750		0.00811		0.0125	

Standard errors in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

In order to correct for this bias, we exploit the fact that countries in our dataset have a price revision period that, in general, does not exceed 36 months (see Table A2 in the Appendix). That is, they periodically revise and update prices of products that are under the scope of ERP criterion of the national regulation. Therefore, we expect the German price variation due to the AMNOG negotiation process to be incorporated in the foreign price revision process within 36 months from the occurrence of the price variation. For this reason, in Table 5 we repeat the analysis but we limit the observations for treated and control products to one to six years after the adoption of the negotiated price in Germany.

6.2 Strategic Effect

As for the strategic spillover effect, Table 6 shows the results of the fixed effect DiD model. The coefficients of the interaction term of the specification as in Equation 4 are equal to 0.0414 (p-value=0.068) if just the product fixed effect is included, to 0.0502

Table 5: Indirect spillover effect calculated from selected observations.

	Fixed Effect DiD Model					
	Lag from negotiated price adoption in Germany					
	1 year	2 years	3 years	4 years	5 years	6 years
	(1)	(2)	(3)	(4)	(5)	(6)
T=1 × Post=1	-0.0347*	-0.0647***	-0.0753***	-0.0753***	-0.0634**	-0.0490
	(0.0178)	(0.0214)	(0.0250)	(0.0282)	(0.0300)	(0.0316)
T=1	-0.169	0.203	-0.192	-0.219*	0.350***	0.339***
	(0.160)	(0.166)	(0.118)	(0.119)	(0.102)	(0.0929)
Post=1	-0.00665	0.00860	0.0420**	0.0590***	0.0542***	0.0465**
	(0.00977)	(0.0146)	(0.0166)	(0.0192)	(0.0197)	(0.0199)
Ln prev	0.0219	0.0136	0.0160	0.0153	0.0147	0.0187
	(0.0378)	(0.0291)	(0.0282)	(0.0288)	(0.0282)	(0.0290)
Ln GDP pc	0.444***	0.412***	0.443***	0.480***	0.492***	0.503***
	(0.130)	(0.0971)	(0.0843)	(0.0756)	(0.0684)	(0.0601)
Launch delay	0.00547	-0.00171	-0.00186	0.000561	0.000187	-0.000452
	(0.00673)	(0.00518)	(0.00441)	(0.00393)	(0.00344)	(0.00308)
Constant	-3.407**	-3.482***	-3.458***	-3.851***	-4.561***	-4.702***
	(1.580)	(1.013)	(1.075)	(0.989)	(0.773)	(0.687)
Product FE	Yes	Yes	Yes	Yes	Yes	Yes
Time FE	Yes	Yes	Yes	Yes	Yes	Yes
Country FE	Yes	Yes	Yes	Yes	Yes	Yes
Observations	2136	3960	5625	7076	8082	8801
R2_within	0.420	0.407	0.428	0.442	0.461	0.472
R2_between	0.0559	0.0737	0.0823	0.0982	0.103	0.0985
R2_overall	0.0359	0.0239	0.0170	0.0180	0.0185	0.0183

Standard errors in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

(p-value=0.033) if product, year and country fixed effects are included, and 0.0548 (p-value=0.021) if, in addition to the fixed effects, we include a set of explanatory variables. Considering the model of Column 3 as the preferred one, we can conclude that the AMNOG reform led to a price increase of 5.48% on prices of foreign products launched in countries that enter the German ERP reference set and that are potentially affected to strategic spillover. That is likely to be a consequence of the effort exerted by manufacturers in the attempt to negotiate a higher price, knowing that it will be directly referenced in Germany and that it will be part of future negotiations through the AMNOG process.

Table 6: Strategic spillover effect of AMNOG reform.

	Fixed Effect DiD model					
Dep. Var.: Ln price	(1)		(2)		(3)	
T=1 × Post=1	0.0414*	(0.0223)	0.0502**	(0.0229)	0.0548**	(0.0232)
T=1	-0.0228	(0.0153)	-0.0276	(0.0279)	0.0805**	(0.0396)
Ln prev					0.0186	(0.0376)
Ln GDP pc					0.235***	(0.0865)
Launch delay					-0.0125**	(0.00559)
Product FE	✓		✓		✓	
Country FE			✓		✓	
Time FE			✓		✓	
Constant	1.311***	(0.0100)	1.375***	(0.0326)	-1.411	(1.102)
Observations	1274		1274		1274	
R^2 within	0.00470		0.158		0.179	
R^2 between	0.0118		0.0199		0.000193	
R^2 overall	0.0199		0.00239		0.0000381	

Standard errors in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Variable Post=1 not shown as there is no variability at the product level: either a product belongs to group Post=1 or to group Post=0.

7 Discussion and Conclusion

In 2011 Germany introduced a new HTA procedure, the new Act to Reorganize the Pharmaceuticals Market (AMNOG), in order to ensure patients' access to the best available medicines while promoting innovation. Under AMNOG legislation, the price of innovative medicines must be negotiated between manufacturers and regulatory bodies, based on two criteria: *i)* the added therapeutic value of the drug with respect to the best alternative available, and *ii)* the EU price level of the product.

The reform has been considered successful in reducing pharmaceutical prices (Lauenroth et al., 2020; Wenzl et al., 2018). However, despite being a domestic reform, AMNOG also influenced prices of neighbour countries. It did so through two spillover mechanisms that, in this case, operate in opposite directions: the indirect spillover effect and strategic spillover effect. The indirect spillover brought by AMNOG affects products launched after German products in ERP countries that refer to Germany. We expect it to be negative because AMNOG effectively reduced domestic prices: as German prices are lower, also prices that explicitly refer to them should be lower, on average. The strategic effect, on the other side, acts in the opposite direction. As we set out in Section 3, we expect the strategic spillover effect to be always positive,

while the indirect effect depends directly on the sign of the price variation caused by the reform. Both our expectations were confirmed by the empirical findings: our DiD analysis showed that, in the period 2011-2017, the indirect spillover effect led to a price reduction of products launched after German products in countries referencing to Germany, in line with previous observations (Lauenroth et al., 2020; Wenzl et al., 2018) and with simulation exercises Stargardt and Schreyögg (2006), after we correct for possible cross-referencing cascade effect to products launched relatively far in time.

On the other side, the strategic spillover effect is associated to a price increase of 5.48% of products in countries referred by Germany that were launched before German products or during the German free-price negotiation-window prescribed by AMNOG legislation. Again, the positive effect confirmed that manufacturers might have exerted more effort in negotiation with foreign countries to affect German prices, confirming the prediction of Mariñoso and colleagues Garcia Mariñoso et al. (2011). At present day, there is no published study that defined and quantified these two mechanisms for the AMNOG reform. Nevertheless, we claim that the strategic effect is entirely due to the presence of ERP in Germany—or, at least, the expectation of its use by the manufacturers—contradicting the common knowledge that the ERP criterion in the AMNOG bill is not used in practice (European Commission, 2015).

To conclude, this work highlights that the design of the domestic pharmaceutical regulation has indeed an impact that goes beyond national borders. If, on one hand, the indirect effect can be intuitive in the ERP context, the strategic effect is more subtle and can harm foreign regulators that are attempting to curb pharmaceutical spending.

8 References

1. GCO. Cancer Today: Estimated number of new cases and mortality in 2020, all cancer, both sexes, all ages. Global Cancer Observatory. https://gco.iarc.fr/today/home, 2020. Accessed: 17-02-2021.

2. S. Vogler, N. Zimmermann, C. Leopold, and K. de Joncheere. Pharmaceutical policies in european countries in response to the global financial crisis. *Southern Medicine Review*, 4(2):69, 2011.

3. C. Rémuzat, D. Urbinati, O. Mzoughi, E. El Hammi, W. Belgaied, and M. Toumi. Overview of external reference pricing systems in Europe. *Journal of Market Access & Health Policy*, 3(1): 27675, 2015.

4. J. Espin, J. Rovira, M. Ewen, and R. Laing. Mapping external reference pricing practices for medicines. *Health Action International and the Andalusian School of Public Health*, 2014.

5. P. Kanavos, A. M. Fontrier, J. Gill, and O. Efthymiadou. Does external reference pricing deliver what it promises? Evidence on its impact at national level. *The European Journal of Health Economics*, 21(1):129–151, 2020.

6. A. P. Holtorf, F. Gialama, K. E. Wijaya, and Z. Kaló. External reference pricing for pharmaceuticals—a survey and literature review to describe best practices for countries with expanding healthcare coverage. *Value in Health Regional Issues*, 19:122–131, 2019.

7. WHO. WHO Guideline on Country Pharmaceutical Pricing Policies. 2013.

8. T. Stargardt and J. Schreyögg. Impact of cross-reference pricing on pharmaceutical prices. *Applied Health Economics and Health Policy*, 5(4):235–247, 2006.

9. A. Richter. Assessing the impact of global price interdependencies. *Pharmacoeconomics*, 26(8):649–659, 2008.

10. K. R. Brekke, A. L. Grasdal, and T. H. Holmås. Regulation and pricing of pharmaceuticals: reference pricing or price cap regulation? *European Economic Review*, 53(2):170–185, 2009.

11. U. Kaiser, S. J. Mendez, T. Rønde, and H. Ullrich. Regulation of pharmaceutical prices: evidence from a reference price reform in Denmark. *Journal of Health Economics*, 36:174–187, 2014.

12. F. Windmeijer, E. De Laat, R. Douven, and E. Mot. Pharmaceutical promotion and GP prescription behaviour. *Health Economics*, 15(1):5–18, 2006.

13. V. D. Lauenroth, A. S. Kesselheim, A. Sarpatwari, and A. D. Stern. Lessons From The Impact Of Price Regulation On The Pricing Of Anticancer Drugs In Germany. *Health Affairs*, 39(7):1185–1193, 2020.

14. D. Ognyanova, A. Zentner, and R. Busse. Pharmaceutical reform 2010 in Germany. *Eurohealth*, 17(1):11–3, 2011.

15. S. Ludwig and C. M. Dintsios. Arbitration board setting reimbursement amounts for pharmaceutical innovations in Germany when price negations between payers and manufacturers fail: an empirical analysis of 5 years' experience. *Value in Health*, 19(8):1016–1025, 2016.

16. J. Ruof, F. W. Schwartz, J. M. Schulenburg, and C. M. Dintsios. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. *The European Journal of Health Economics*, 15(6):577–589, 2014.

17. V. D. Lauenroth and T. Stargardt. Pharmaceutical pricing in Germany: how is value determined within the scope of AMNOG? *Value in Health*, 20(7):927–935, 2017.

18. M. Wenzl, V. Paris, et al. Pharmaceutical reimbursement and pricing in Germany. *OECD (Ed.)*, 1:22, 2018.

19. V. Paris and A. Belloni. Value in pharmaceutical pricing. Technical report, OECD Health Working Paper, Paris, France, 2013.

20. European Commission. Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. final report. 2015.

21. Margaret K Kyle, David B Ridley, and Su Zhang. Strategic interaction among governments in the provision of a global public good. *Journal of Public Economics*, 156:185–199, 2017.

22. C. Leopold, S. Vogler, A. Mantel-Teeuwisse, K. de Joncheere, R. Laing, and H. Leufkens. Impact of external price referencing on medicine prices–a price comparison among 14 european countries. *Southern Medicine Review*, 5(2):34, 2012.

23. M. Csanádi, Z. Kaló, C. Prins, E. Grélinger, M. M. Kiss, F. U. Fricke, L. Fuksa, T. Tesar, M. Manova, L. Lorenzovici, et al. The implications of external price referencing on pharmaceutical list prices in Europe. *Health Policy and Technology*, 7(3):243–250, 2018.

24. Zoltán Kaló, Ibrahim Alabbadi, Ola Ghaleb Al Ahdab, Maryam Alowayesh, Mahmoud Elmahdawy, Abdulaziz H Al-Saggabi, Vito Luigi Tanzi, Daoud Al-Badriyeh, Hamad S Alsultan, Faleh Mohamed Hussain Ali, et al. Implications of external price referencing of pharmaceuticals in middle east countries. *Expert review of pharmacoeconomics & outcomes research*, 15(6): 993–998, 2015.

25. P. Kanavos, A. M. Fontrier, J. Gill, O. Efthymiadou, and N. Boekstein. The impact of external reference pricing within and across countries. 2017.

26. M. Toumi, C. Remuzat, A. L. Vataire, and D. Urbinati. External reference pricing of medicinal products: simulation-based considerations for cross-country coordination. *Final Report. European Commission*, 14:2014, 2014.

27. S. Vogler, P. Schneider, and L. Lepuschütz. Impact of changes in the methodology of external price referencing on medicine prices: discrete-event simulation. *Cost Effectiveness and Resource Allocation*, 18(1):1–9, 2020.

28. S. Merkur and E. Mossialos. A pricing policy towards the sourcing of cheaper drugs in Cyprus. *Health Policy*, 81(2-3): 368–375, 2007.

29. L. Maini and F. Pammolli. Reference pricing as a deterrent to entry: Evidence from the European pharmaceutical market. *Available at SSRN 3694471*, 2020.

30. M. K. Kyle. Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics*, 89(1):88–99, 2007.

31. Jenny Lanjouw. Patents, price controls, and access to new drugs: how policy affects global market entry, 2005.

32. P. Danzon, Y. R. Wang, and L. Wang. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. *Health Economics*, 14(3):269–292, 2005.

33. A. Heuer, M. Mejer, and J. Neuhaus. The national regulation of pharmaceutical markets and the timing of new drug launches in Europe. Technical report, Kiel Advanced Studies Working Papers, 2007.

34. D. N. Lakdawalla. Economics of the pharmaceutical industry. *Journal of Economic Literature*, 56(2):397–449, 2018.

35. B. Garcia Mariñoso, I. Jelovac, and P. Olivella. External referencing and pharmaceutical price negotiation. *Health Economics*, 20(6):737–756, 2011.

36. D. Geng and K. Saggi. International effects of national regulations: External reference pricing and price controls. *Journal of International Economics*, 109:68–84, 2017.

37. L. Birg. External reference pricing and the choice of country baskets and pricing rules. Technical report, cege Discussion Papers, 2016.

38. Nicolas Houy and Izabela Jelovac. Drug launch timing and international reference pricing. *Health economics*, 24(8):978–989, 2015.

39. A. Muthoo. *Bargaining theory with applications*. Cambridge University Press, 1999.

40. P. Pertile, S. Gamba, and M. Forster. Free-riding in pharmaceutical price regulation: Theory and evidence. 2018.

41. Angela B Mariotto, K Robin Yabroff, Yongwu Shao, Eric J Feuer, and Martin L Brown. Projections of the cost of cancer care in the united states: 2010–2020. *Journal of the National Cancer Institute*, 103(2):117–128, 2011.

42. Thomas Hofmarcher, Peter Lindgren, Nils Wilking, and Bengt Jönsson. The cost of cancer in europe 2018. *European Journal of Cancer*, 129:41–49, 2020.

43. T. Vos, C. Allen, M. Arora, R. M Barber, Z. A Bhutta, A. Brown, A. Carter, D. C Casey, F. J Charlson, A. Z Chen, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. *The lancet*, 388 (10053):1545–1602, 2016.

44. Margaret Kyle and Yi Qian. Intellectual property rights and access to innovation: evidence from trips. Technical report, National Bureau of Economic Research, 2014.

45. Antonio Cabrales and Sergi Jiménez-Martín. The determinants of pricing in pharmaceuticals: Are us prices really so high? *Health economics*, 22(11):1377–1397, 2013.

46. Jaume Puig-Junoy and Beatriz González López-Valcárcel. Launch prices for new pharmaceuticals in the heavily regulated

and subsidized spanish market, 1995–2007. *Health Policy*, 116(2-3):170–181, 2014.

47. J. Pontén, G. Rönnholm, and P. Skiöld. PPRI Pharma Profile Sweden. *Vienna: Pharmaceutical Pricing and Reimbursement Information (PPRI)*, 2017.

48. D. Kullman. PHIS Hospital Pharma Report United Kingdom. *Vienna: Gesundheit Österreich GmbH/Geschäftsbereich ÖBIG*, 2010.

49. J. Gill, A. M. Fontrier, D. Kyriopoulos, and P. Kanavos. Variations in external reference pricing implementation: does it matter for public policy? *The European Journal of Health Economics*, 20(9):1375–1397, 2019.

50. S. Vogler, N. Zimmermann, and M. A. Haasis. PPRI Report 2018-Pharmaceutical pricing and reimbursement policies in 47 PPRI network member countries. WHO Collaborating Centre for Pricing and Reimbursement Policies. 2019.

A Appendix

Table A1: Each product's descriptive statistics.

Product	*Avg*	*SD*	*Launch*	*(1)*	*Product*	*Avg*	*SD*	*Launch*	*(1)*
Abraxane	2.85	0.41	2005q1	12	Lonsurf	7.33	6.05	2014q2	11
Adcetris	67.46	10.44	2011q3	18	Lynparza	0.25	0.07	2014q4	17
Afinitor	12.37	4.37	2009q1	18	Mekinist	111.37	28.16	2013q2	12
Arzerra	2.47	1.00	2009q4	17	Nexavar	0.16	0.00	2005q4	3
Atriance	1.29	0.12	2006q1	15	Ninlaro	660.41	32.68	2015q4	6
Avastin	3.05	0.11	2004q1	1	Odomzo	1.53	0.04	2015q3	1
Blincyto	74034.45	8648.58	2014q4	14	Onivyde	16.50	0.00	2015q4	1
Bosulif	0.31	0.09	2012q3	18	Opdivo	17.84	9.62	2014q3	19
Cabometyx	4.63	1.71	2016q2	6	Perjeta	6.63	1.09	2012q2	19
Caprelsa	0.61	0.26	2011q2	19	Pixuvri	21.08	5.12	2012q2	9
Cometriq	1.67	0.77	2013q1	9	Portrazza	2.44	1.16	2015q4	7
Cotellic	4.49	0.40	2015q3	11	Spectrila	32.47	22.43	2016q3	2
Cyramza	6.12	1.22	2014q2	16	Sprycel	0.94	0.11	2006q3	12
Dacogen	22.65	5.25	2006q2	15	Stivarga	1.25	0.62	2012q3	19
Darzalex	4.85	0.60	2015q4	11	Sutent	3.39	0.30	2006q1	4
Empliciti	4.31	0.69	2015q4	10	Tafinlar	0.75	0.18	2013q2	21
Erbitux	2.04	0.43	2004q1	3	Tagrisso	3.02	0.88	2015q4	11
Erivedge	1.47	0.39	2012q1	15	Targretin	0.27	0.01	2000q1	1
Evoltra	47.33	3.27	2005q1	1	Tasigna	0.16	0.04	2007q3	18
Farydak	38.37	9.82	2015q1	10	Teysuno	0.09	0.01	2011q1	14
Gazyvaro	3.79	0.49	2013q4	20	Torisel	28.66	2.97	2007q2	14
Giotrif	1.77	0.82	2013q3	22	Trisenox	36.75	7.19	2000q4	9
Halaven	451.19	154.08	2010q4	17	Tyverb	0.07	0.01	2007q1	15
Ibrance	2.17	0.99	2015q1	10	Unituxin	448.93	97.82	2015q2	2
Iclusig	5.25	1.77	2012q4	15	Vargatef	0.21	0.04	2014q4	13
Imbruvica	0.50	0.09	2013q4	17	Vectibix	4.17	0.59	2006q4	18
Imlygic	26.29	7.42	2015q4	8	Venclyxto	0.62	0.10	2016q2	8
Inlyta	14.21	5.34	2012q1	22	Vidaza	3.62	0.41	2004q2	12
Iressa	0.30	0.03	2002q3	16	Votrient	0.13	0.04	2009q4	22
Jakavi	3.71	1.17	2011q4	22	Xalkori	0.37	0.13	2011q3	20
Javlor	4.26	0.91	2009q3	12	Xaluprine	0.01	0.00	2012q1	11
Jevtana	72.84	18.18	2010q3	20	Yervoy	83.94	11.47	2011q1	22
Kadcyla	18.10	2.64	2013q1	21	Yondelis	1816.10	347.20	2007q4	16
Keytruda	34.87	3.84	2014q3	19	Zaltrap	4.57	2.83	2012q3	17
Kisplyx	6.39	0.85	2016q3	5	Zelboraf	0.14	0.03	2011q3	20
Kyprolis	21.96	3.22	2012q3	16	Zydelig	0.49	0.14	2014q2	16
Lenvima	6.23	0.71	2015q1	15	Zykadia	0.30	0.11	2014q2	16

Table A2: ERP implementation in Europe: latest data available.

Country	*Criterion*	*Price*	*Basket*	*Benchmark price*	*Disc.*	*Revision frequency*	*(1)*
Austria	main	ex-factory	26	average	no	ad hoc	all
Belgium	supportive	ex-factory	27	average	no	at launch only	in patent
Bulgaria	main	ex-factory	17	minimum	no	Reimb. med.: every 6 m. Non reimb.: at launch only	all
Croatia	main	PPP	3 out of 5	average	no	12	
Cyprus	main	PPP	4 out of 10	average	no	12	
Czech Rep.	main	ex-factory	18	average of 3 lowest	no	12	all
Estonia	main	ex-factory	3	Price cannot exceed the highest price in the basket	no	Outpatient: dep. on agreement. Inpatient: annually	in patent
Finland	supportive	PPP	30	average	no	60	
France	supportive	ex-factory	4	Prices similar to basket and not lower than the lowest	no	Every 4–5 years	in patent
Germany	supportive	ex-factory	15	Weighted based on mkt size and PPP	yes	At launch and if new evidence available	in patent
Greece	main	ex-factory	27	average of 3 lowest	no	Biannual in first 4 years	in patent
Hungary	main	ex-factory	30	minimum	no	at launch only	in patent
Iceland	main	PPP	4	average	no	24	
Ireland	supportive	ex-factory	14	average	no	36	
Italy	supportive	ex-factory	25	average	no	ad hoc	in patent
Latvia	supportive	ex-factory	7	third lowest price	no	24	all
Lithuania	supportive	ex-factory	27	average	no	12	
Luxembourg	main	ex-factory	origin	minimum	no	12	
Malta	main	ex-factory	12	average	no	18	
Netherlands	main	PPP	4	average	no	6	
Norway	main	PPP	9	average of 3 lowest	no	12	
Poland	supportive	ex-factory	30	minimum	no	Every 2, 3, or 5 years)	all
Romania	main	ex-factory	12	minimum	no	12	all
Slovakia	main	ex-factory	27	average of 3 lowest	no	6	all
Slovenia	main	ex-factory	3	minimum	no	6	all
Spain	supportive	ex-factory	14	minimum	no	24	in patent
Switzerland	supportive	ex-factory	9	average	no	36	
Russia	main	PPP	12	minimum		At manufacturers' request	all
Turkey	main	ex-factory	5	minimum		n/a	in patent
Sweden	no						
UK	no						

(1): Medicine patent status. Data from Gill et al. (2019), Kanavos et al. (2020), Vogler et al. (2019), Vogler et al. (2020).