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Preface

The pharmaceutical sector is among the most regulated industries worldwide. Before receiving market authorization, all products must undergo a well-defined procedure in which the relevant supranational authorities (*i.e.* the Federal Drug Administration in the United States and the European Medicine Agency in the European Union) ensure that specific safety and efficacy standards are met. Nevertheless, the advancements over the years have been significant, with several examples of cutting-edge life-saving treatments that would have been inconceivable in the past—immunotherapy for cancer, gene therapy and precision medicine, to name a few. Hand in hand with pharmaceutical breakthroughs, however, comes the rise of the price of new medicines. In the European Union, where healthcare systems are mostly public and universal, national regulators face the challenge of guaranteeing affordable access to the newest treatments available with tighter budget constraints. For this reason, they often rely on a "fourth hurdle" for the approval of new pharmaceuticals: in addition to safety, efficacy, and quality requirements, every new product must demonstrate that the benefits generated are worth the price that is reimbursed by the public payer, based on objective health technology assessments (HTA). To some extent, this is akin to an indirect form of price control, where regulatory agencies seek to curb expenditures and, in addition, to align the cost of new innovative treatments with their added therapeutic benefits.

Alternatively to (or on top of) the HTA evaluation process, which requires technical expertise and costly infrastructure, a national regulator can simply set other countries' prices as a benchmark to determine whether new medicines are worth the price paid domestically. This criterion is also referred to as external reference pricing (ERP) or international reference pricing (IRP). ERP criteria have been quite attractive due to their simplicity, but they embed a crucial drawback: they create a mechanism of complex interdependencies across national price regulations, where countries reference to and, at the same time, are referenced by foreign regulators. In partial fulfillment of my Ph.D., I address the impact of introducing HTA and the role of such interplay across regulations, following a combination of theoretical and empirical approaches.

In particular, in the first Chapter, I show that more stringent regulations have successfully reduced the prices of anticancer drugs in Germany. I used a triple difference approach to estimate the causal effect of the AMNOG reform in 2011. The bill introduced a round of negotiation between pharmaceutical firms and the German regulator based on the added therapeutic benefit of the drug and the price level of a well-defined set of countries (the ERP criterion).

The second Chapter takes a theoretical perspective to delve into the consequences of the interplay across different national pharmaceutical price regulations. Crucially, the wide adoption of ERP schemes is generally believed to create negative externalities for the pharmaceutical industry due to the tendency of low prices to propagate to high-priced markets through ERP provisions. In other words, the more frequently ERP criteria are adopted across national regulations, the less the pharmaceutical industry is able to price-discriminate across markets. Nevertheless, firms can counteract this negative impact by strategically delaying the launch of new medicines in low-income markets—thus preventing low prices from propagating—or by restoring their ability to price discriminate with a combination of higher "list" prices and substantial secret discounts. Nevertheless, there is growing public pressure advocating for more transparency. The second Chapter contributes to this ongoing debate. I show that a ban on confidential discounts—aimed at restoring the firm's ability to price discriminate—would disproportionately benefit the ERP adopter, at the expense of the firm and of the country whose prices are considered as benchmarks by the ERP adopter itself. However, total Welfare would ultimately increase with fully transparent ERP schemes.

Finally, the third Chapter (co-authored with Paolo Pertile and Simona Gamba) provides evidence of the price increase in countries that are included in the ERP list of a national regulator. In particular, we employ the same reform used for the first Chapter, exploiting the ERP criterion embedded in the AMNOG reform. Our empirical analysis uses a dataset of 65 cancer drugs in 16 countries and, in line with our predictions and the related literature, confirms that pharmaceutical firms have raised the price, on average, by 6.7% in countries that serve as a benchmark for the German regulator in negotiating the domestic price. To the best of our knowledge, this is the first empirical contribution to the literature and represents the present work's most novel finding.

Chapter 1

The Impact of AMNOG on German Prices

G. Righetti

Abstract *In years of growing pharmaceutical spending, the provision of innovative medicines faces stricter budgetary constraints. The response in the European Union (EU) has been to rely on health technology assessment (HTA) in order to align the cost of new innovative treatments with their added therapeutic benefits. I analyze the impact of the AMNOG reform in Germany in 2011 on pharmaceutical prices. The bill introduced a mandatory price negotiation process based, among other criteria, on the added therapeutic value of the new medicine. I employed a triple difference analysis, exploiting the IMS pricing database of 85 anticancer drugs launched between 2007 and 2017 in 24 OECD countries. I confirm the success of the AMNOG reform: the negotiation process introduced in 2011 has successfully reduced drug prices by 16.4%.*

Keywords AMNOG, pharmaceutical regulation, HTA, Triple differences

JEL codes I10, I18

1.1 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). The majority of EU countries complement price control approaches with the reliance on health technology assessment (HTA) processes to design their reimbursement schemes (Angelis et al., 2018). Although national HTA bodies can lead to very heterogeneous recommendations over the same treatment (Akehurst et al., 2017), their aim is always to evaluate the additional benefit of new pharmaceuticals over existing comparators and to inform the decision-maker with evidence-based assessment reports. Notably, the World Health Organization (2015) has called for a more extensive reliance on HTA to provide comprehensive and transparent supplementary evidence that is able to capture additional dimensions of value. In addition, European Regulators often adhere to external reference pricing (ERP) criteria to avoid overpaying for new medicines with respect to their neighbors (Espin et al., 2014; Kanavos et al., 2020; Rémuzat et al., 2015).[1]

The German Federal Parliament (Bundestag) introduced, in 2011, a new HTA procedure, the Act to Reorganize the Pharmaceuticals Market (AMNOG).[2] The new bill put forward evidence-based evaluations of new drugs in relation to the standard of care, in order to ensure patients' access to the best available medicines while promoting innovation (Greiner et al., 2023). Until then, rather exceptionally in an international comparison, manufacturers were largely free to set prices for new drugs in Germany. Instead, the new legislation grants firms that obtain the European Medicine Agency (EMA) approval the freedom to set the price of the new drug as it had been before the reform, but limited to the first twelve months since market entry. Hereafter, I refer to the—temporary—freely set price as the *unregulated* price. After these twelve months, firms must adhere to the price that they agreed upon during the negotiation process, as prescribed by the AMNOG bill. Specifically, the price negotiation is conducted between the manufacturer of the innovative medicine and regulatory bodies based on: *i)* the price of the closest comparator, if available; *ii)* the added therapeutic value of the drug; and *iii)* the price level of the product in a bundle of pre-determined countries. Because of the reliance on international prices as one of the criteria on which price negotiations are undertaken, German pharmaceutical regulation is also regarded as having a "mild" form of ERP (Rémuzat et al., 2015). Hereafter, I refer to the price that emerges after the negotiation

[1] ERP criteria consist of using the price of new medicine in one or several countries in order to derive a reference price, which is then used in setting or negotiating the price of the product (WHO, 2013). In general, their actual implementation can be quite heterogeneous (Gill et al., 2019).

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

process as the *regulated* price.

In general, German regulated prices are found to be correlated with the added benefit brought by the treatment, while unregulated prices are not (Lauenroth et al., 2020). Moreover, Lauenroth et al. (2020) observe that regulated prices are on average 24.5% lower than unregulated prices, in line with the figures reported by Greiner et al. (2023). As an unintended consequence of the general price reduction induced by the reform, Büssgen and Stargardt (2022) found that the AMNOG negotiation process led to a launch delay of 4.31 months in Germany compared to control countries. That aligns with the evidence on the correlation between more stringent regulation and strategic launch delay (Cockburn et al., 2016; Danzon et al., 2005; Heuer et al., 2007; Maini and Pammolli, 2023).[3] The role played by international prices on the AMNOG negotiation process has been investigated by Lauenroth and Stargardt (2017): they found that indeed the EU price level is correlated with the price premium of the innovative drug under the scope of AMNOG. Although significant, this effect is rather small.[4] It is accepted that the explicit and widespread reliance on ERP criteria can lead to a downward price convergence over time and across countries. This has been supported by a number of simulation exercises (Merkur and Mossialos, 2007; Toumi et al., 2014; Vogler et al., 2020) and it has been shown empirically by Leopold et al. (2012) and Csanádi et al. (2018).

The present work aims to quantify the AMNOG reform's effect on pharmaceutical prices in Germany. To the best of the author's knowledge, no previous study causally assessed the price impact of the AMNOG reform. For this purpose, I use data from the IMS pricing database, covering quarterly prices of anticancer drugs approved by the European Medicine Agency (EMA) and launched in 24 OECD countries from 2007 to 2017.[5] I employ a triple difference approach that exploits the specific features of the bill to infer the causal relationship between the AMNOG reform and pharmaceutical prices, showing that the reform successfully delivered a price reduction for anticancer drugs in Germany.

The remainder of Chapter 1 is structured as follows: Section 1.2 reviews in detail the reform in pharmaceutical regulation that occurred in Germany in 2011; Section 1.3 sets out the method used; Section 1.4 provides a brief overview of the data employed; Section 1.5 outlines and comments the results obtained. Finally, Section 1.6 summarizes the findings and concludes the work.

[3] In a context where ERP regulations are widely implemented, this might be due to the attempt by manufacturers to avoid the cross-country propagation of lower "regulated" prices to reference countries (Houy and Jelovac, 2015). In the present analysis, I set aside from launch timing consideration, although I acknowledge that it might be intertwined with the price dimension. This issue is discussed in Section 1.6 and, in more detail, in Chapter 2.

[4] They report that an increase in the European price level of €1 per defined daily dose was associated with a significant increase in the price premium ranging from 0.06% to 0.13%.

[5] Following the merge between IMS Health and Quantiles, IMS has been renamed IQVIA.

1.2 Institutional Background

Germany spends a greater proportion of its GDP on health (12.7%) than any other EU country (OECD, 2023) and has one of the highest per capita pharmaceutical spending worldwide: in 2021, it spent USD 1,006 per capita, corresponding to the highest value in the EU and 64% more than the OECD average (OECD, 2023). Prior to 2011, pharmaceutical manufacturers could freely set the price once EMA granted market authorization. This led to an estimated EUR 7.4 billion deficit for 2010 and EUR 11 billion for 2011 for the German Health Insurance System (SHI) (Ludwig and Dintsios, 2016), inducing the German legislator to carry out an HTA reform in 2011, the new Act to Reorganize the Pharmaceuticals Market (AMNOG). The aim was to curb expenditure, ensure patients' access to the best available medicines and to promote innovation.[6] The new HTA procedure establishes that manufacturers that obtain EMA approval to launch new drugs are initially free to set prices with no restrictions for twelve months. However, within three months since market entry, the manufacturer must also submit a dossier to the Federal Joint Committee (G-BA), the key legal institution of the self-administered German healthcare system, to prove the additional benefit of the drug over the appropriate comparator.[7] The G-BA has three months to to assess the dossier; then, it determines additional benefits along six categories: major, considerable, minor, non-quantifiable (comprising major, considerable or minor, but the data may be preliminary), no benefit, and less benefit.[8]

Pharmaceuticals that do not offer additional therapeutic benefits are directly included in Germany's (internal) reference pricing system, as before the reform. Instead, medicines that do demonstrate a clinical added value are subject to price negotiations between the Federal Association of Sickness Funds (SHI) and the manufacturer. Orphan drugs are excluded from the obligation of benefit assessment after licensing only if sales are not expected to exceed EUR 50 million per year (Greiner et al., 2023). The negotiating parts must 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 initially by the manufacturer. In case no agreement is reached, an Arbitration Board reexamines the case and takes its final decision within three months.[9]

[6] This was preceded by a number of legal reforms with approaches of cost containment but without the intention of implementing a benefit assessment of pharmaceuticals, such as a price freeze to keep the same price level as of 2009 until the end of 2017 (Ludwig and Dintsios, 2016).

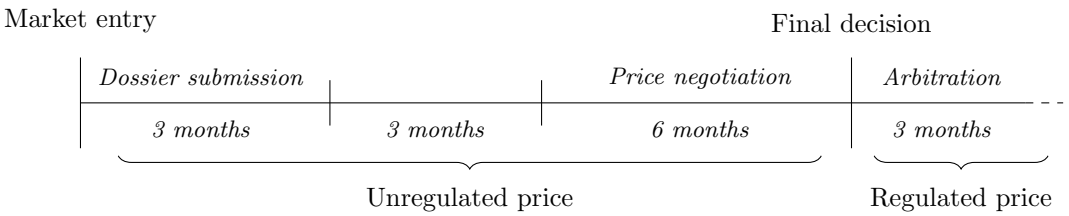
[7] The Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA) is the highest German decision-making body of the joint self-governing board of stakeholders in healthcare, formed by physicians, dentists, hospitals and health insurance funds.

[8] Alternatively, the G-BA can request the Institute for Quality and Efficiency in Health Care (IQWiG) to perform the assessment.

[9] Until 2015, 15% of negotiations ended up in the arbitration stage (Ludwig and Dintsios, 2016).

The steps are summarized in Figure 1.1. During the negotiation process, stakeholders and

Figure 1.1: AMNOG process for German innovative medicines



decision-making bodies must take into account: *i)* the price of the available comparator, if available; *ii)* the added value of the innovative drug with respect to the available comparator; and, as a supportive criterion, *iii)* the prices paid in other European countries (External reference pricing criterion). In particular, the benchmark 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. Countries included are Belgium, Denmark, Finland, France, UK, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Spain, and the Czech Republic.[10] Finally, it should be highlighted that AMNOG regulation is not retroactive, and only products launched after 2011 undergo price negotiations. What is crucial for the identification strategy of the empirical analysis conducted in Section 1.3 is the clear distinction between the unregulated free price that lasts for the first 12 months and the regulated price that emerges since the 13$^{\text{th}}$ months, after the conclusion of the negotiation process.

From 2011, when AMNOG entered into force, to mid-March 2021, 291 drugs with a new active substance or combination of active substances were subjected to an early benefit assessment by the G-BA. Of those drugs, 32% treated various forms of cancer (Greiner et al., 2023). Of all active substances evaluated, 64% were able to demonstrate an additional benefit in at least one therapeutic area. As for oncology drugs, an additional benefit was identified for only 52% of all initial assessments (Greiner et al., 2023).

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

1.3 Empirical Model

To detect the effect of the AMNOG reform on German pharmaceutical prices, I employed a difference-in-difference-in-difference (DDD or triple difference) framework. First, for each German product launched after the 2011 reform, I compare the regulated prices (those resulting from the AMNOG negotiation process, as defined in Section 1.1) with the unregulated prices set by manufacturers. This raw comparison would quantify how much regulated prices, as agreed by stakeholders, differ from unregulated prices, as initially set by firms. On average, I expect the regulated prices to be 20%-25% lower than unregulated prices in Germany (Greiner et al., 2023; Lauenroth et al., 2020). However, it might be the case that even before 2011, products were prone to experience price reductions over time, especially 12 months after market entry. Among the reasons are: product's obsolescence (Kanavos and Vandoros, 2011; Puig-Junoy and López-Valcárcel, 2014); competition from parallel distributors (Brekke et al., 2015; Dubois and Sæthre, 2020; Duso et al., 2014); and growing therapeutic competition from other existing products (Danzon and Epstein, 2008; Kanavos et al., 2007).[11] Those factors can be especially relevant in areas where the innovation pace is growing rapidly. If that is the case, the effect resulting from this first comparison would likely overestimate the impact of the reform on prices.

To account for that, I subtract from the first comparison the same difference but referred to products launched in Germany before 2011 (second comparison). In the strictest sense, prices of products that entered the German market before the AMNOG reform are all unregulated. Therefore, the distinction between unregulated and regulated prices that holds for post-2011 products boils down, for symmetry, to the distinction between prices observed within 12 months since market entry and after the 13^{th} month after market entry for pre-2011 products.[12] In this way, the resulting (intermediate) difference-in-differences would cancel out any common price trend across each product's life cycle. This second comparison relies on the assumption that the unregulated prices after 2011 are not affected by the reform—that is, there is no anticipation effect. Although there is already some evidence in that direction (Lauenroth et al., 2020), this is further discussed in Section 1.5. However, the empirical analysis might still be biased if the downward price trend common to each product changes over time across all economies. If true, the result would be, again, overestimated.

This is addressed by including a third comparison, which involves the price of German

[11] I exclude generic competition since in the analysis I only consider products under patent protection.

[12] Note that, as mentioned in Section 1.2, the AMNOG regulation is not retroactive. That implies that once a drug is launched in Germany, its treatment status only depends on the launch date (either before or after 2011) and does not switch after 2011. In other words, products launched before 2011 are never subject to the AMNOG negotiation process.

drugs and the price of drugs launched in a set of other countries, denoted as "control countries". Specifically, this last comparison aims to eliminate all variation due to price trends common to all economies across products and over time. The key issue in the choice of control countries is related to the potential cross-referencing that comes from the wide adoption of ERP schemes in the EU (Espin et al., 2014). In fact, depending on the composition of each country's ERP basket of reference countries, either prices in control countries are responsive to German prices, or prices set in countries included in the German reference set will contribute to the determination of the negotiated price in Germany, or both (Stargardt and Schreyögg, 2006; Toumi et al., 2014).[13] In particular, countries that explicitly rely on prices set in Germany among their price-setting criteria for pharmaceuticals are potentially responsive to changes in German prices. If that is the case, even assuming that the way they are affected by German prices has not changed over time, the identification would still underestimate the true effect of the AMNOG reform since the control prices would, in fact, be affected by German prices. If, on the other side, German prices indeed depend on the prices set in countries included in the German ERP bundle, as prescribed by the AMNOG legislation, the identification would still be biased, but the direction of the bias would remain ambiguous. This is discussed in Section 1.5.1, where different exclusion criteria for the selection of the control countries are adopted. The combination of the first, second and third comparison comprises the triple difference framework, on which the analysis is based. In this light, I set the following empirical model (Equation 1.1):

$$\begin{aligned} y_{ict} =& \beta_0 + \beta_1 Post_t + \beta_2 Ger_c + \beta_3 Reg_{it} + \\ &+ \beta_4 (Post_t \times Ger_c) + \beta_5 (Post_t \times Reg_{it}) + \beta_6 (Ger_c \times Reg_{it}) + \\ &+ \beta_7 (Post_t \times Ger_c \times Reg_{it}) + \beta_8 \mathbf{X}_{ct} + \theta_i + \delta_t + \gamma_c + \varepsilon_{ict} \end{aligned} \tag{1.1}$$

The dependent variable y_{ict} is the natural logarithm of the price of product i for country c at time t (time is in quarters of a year). Reg_{it} is equal to 1 when the observation for product i refers to a regulated price and equal to 0 when it refers to an unregulated price. Notice that, for symmetry and parsimony, the distinction also applies to products launched before 2011: in that case, the price observation in t is associated with $Reg_{it} = 0$ if the price observation lies in the first 12 months since the launch of product i, whereas is associated with $Reg_{it} = 1$ if it lies after the 13^{th} months. $Post_t$ is a dummy indicating whether the first price observation available for product i occurred after 2011 ($Post_t = 1$). Ger_c is a dummy indicating whether

[13] In Chapter 3 a closely related issue is explored: exactly because the prices set in countries included in the German reference set contribute to the determination of the negotiated prices in Germany, manufacturers have the incentive to inflate prices in those countries after reform.

country c is Germany. The coefficient of interest is of the triple interaction term between Reg_{it}, $Post_t$ and Ger_c, so that it can be interpreted as the triple difference estimator of the impact of the AMNOG reform on German prices. Three fixed effects are also included. The time fixed effect δ_t controls for unobserved shocks over time that are common to all products and countries. The product fixed effect θ_i captures the unobserved drug i's quality and therapeutic advance, which can be a primary driver of prices and strongly differ across products. Finally, the country fixed effect γ_c captures time-invariant differences in prices among countries.

The explanatory variables that are employed are those potentially relevant to the price negotiation dynamic. GDP_{ct} is the GDP per capita at time t in country c, in order to account for how much the national payer is willing to pay the manufacturer (Cabrales and Jiménez-Martín, 2013; Kyle and Qian, 2014; Leopold et al., 2012; Pertile et al., 2018). I expect that 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). $lnPREV_{ict}$ is the natural logarithm of prevalence of product i in country c at time t. Prevalence is intended as a proxy for market size, as it can capture the potential impact of this variable on price negotiations. The correlation between market size and pharmaceutical prices has been explored both theoretically and empirically (Egan and Philipson, 2013; Kyle and Qian, 2014; Puig-Junoy and López-Valcárcel, 2014), but the evidence is not conclusive (Pertile et al., 2023). Differently from Puig-Junoy and López-Valcárcel (2014), however, who measured market size as the defined daily doses sold by competitors the previous year, I consider the prevalence as the number of individuals with a specific condition that is targeted by product i at time t in country c (Maini and Pammolli, 2023; Pertile et al., 2018). Finally, $PRODAGE_{it}$ represents the measure for the age of product i at time t, taking as baseline the first entry of the same product worldwide. Product's age is a measure of obsolescence and it is expected to be inversely related to drug prices (Kanavos and Vandoros, 2011; Puig-Junoy and López-Valcárcel, 2014).

1.4 Data

The empirical analysis is conducted by exploiting the Pricing Insights IMS database.[14] I rely on information on quarterly prices and on the date of launch for a total of 85 anticancer drugs authorized by EMA from 2007 to 2017 in 24 OECD countries.[15] Table A.1.1 in the Appendix

[14] Following the merge between IMS Health and Quantiles, IMS has been renamed IQVIA.

[15] Data on quarterly prices and information on the date of launch were initially retrieved for a total of 108 antineoplastic (anticancer) drugs authorized by EMA from 1995 to 2017. However, 23 of these had to be excluded: 6 do not treat cancer, 3 do not have prevalence data, 2 are hybrid drugs, and 12 were not on patent. Also, the data set initially comprised a total of 25 countries that, in 2007, were members of the OECD.

lists all countries considered in the analysis, reporting whether they rely on ERP among the criteria for their price regulation and whether the AMNOG legislation includes them in the bundle of reference countries.

Anticancer products were chosen as they have driven the increase in pharmaceutical expenditure worldwide (Hofmarcher et al., 2020; Mariotto et al., 2011). Nevertheless, the products considered are heterogeneous in terms of average price, and they have not been launched uniformly: Table A.1.2 in the Appendix sketches the descriptive statistics of all products that enter the analysis, with their first entry date across all markets considered in the dataset. All prices are converted into Euro using the quarterly exchange rate reported in the IMS database. Also, all prices have been harmonized and refer to a milligram of active substance. This choice intends to make products sold with different pack sizes or strengths comparable within and across countries. Moreover, when different prices are available for the same product, and at the same time within one country, the lowest available price per milligram is considered.[16] Data for prevalence are extracted from the Global Burden of Diseases (GBD) 2015 database (Vos et al., 2016). Specifically, I referred to EMA therapeutic indications of the drug and matched them with the associated prevalence as indicated in the GBD database.[17] 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-year intervals, therefore prevalence is assumed to remain constant within that time interval. Finally, data for GDP per capita are extracted from the World Bank Indicators and converted into Euro with the exchange rate in the IMS database. The variables employed and their sources are listed in Table 1.1 below.

Table 1.1: Variables employed in the empirical analysis

Variable	*Type*	*Definition*	*Source*
Ln Price	cont.	Natural log of quarterly price per mg	Pricing Insights IMS database
Timesince	cont.	Time in months since the product launch in the first country of launch.	Pricing Insights IMS database
Ln prev	cont.	Natural log of prevalence of diseases treated by product i in country c.	GBD 2015 database
Ln GDP pc	cont.	Natural log of GDP per capita.	World Bank Indicator

However, Portugal was omitted because the Pricing Insights IMS Health database provides only very partial coverage for that period.

[16] 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%).

[17] I relied on the highest level of detail (level 3) as captured by the GBD database. See Vos et al. (2016) for the details.

1.5 Results

Results for the analysis of the impact of AMNOG on German prices, with robust standard errors clustered at the product level, are shown in Table 1.2. In particular, the Table shows

Table 1.2: Effect of AMNOG on German prices/1

	All observations		*Not in AMNOG ERP*	
Dep. Var.: Ln Price	(1)	(2)	(3)	(4)
Ger × Post × Reg	-0.177***	-0.164***	-0.198***	-0.155***
	(0.043)	(0.044)	(0.048)	(0.053)
Ger × Post	-0.006	-0.020	0.062	0.015
	(0.030)	(0.031)	(0.043)	(0.052)
Ger × Reg	-0.001	-0.013	-0.029	-0.070**
	(0.013)	(0.015)	(0.026)	(0.035)
Post × Reg	0.004	0.003	0.042	0.043
	(0.016)	(0.016)	(0.035)	(0.037)
Ln prev		-0.008		-0.023
		(0.020)		(0.018)
Ln GDP pc		0.195***		0.501***
		(0.063)		(0.123)
Prod Age		-0.013***		-0.012**
		(0.003)		(0.006)
Constant	1.050***	-0.909	1.207***	-3.872***
	(0.019)	(0.726)	(0.038)	(1.354)
Prod, Year, Country FE	Yes	Yes	Yes	Yes
Observations	15124	15124	5652	5652
R^2 adj.	0.994	0.994	0.994	0.994

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

the preferred models without the inclusion of covariates (Column 1) and with their inclusion (Column 2). In addition, it reports the models that only consider price observations of products launched in countries that are not included in the AMNOG's ERP criterion, without covariates (Column 3) and with their inclusion (Column 4). Columns 3 and 4 are meant to rule out the bias from the dependency of German prices on prices set by countries included in the AMNOG's ERP bundle. Considering only models with covariates (Columns 2 and 4 of Table 1.2), it is possible to observe that they both present negative and significant coefficients for the triple interaction term of interest: -0.164 and -0.155, respectively. It appears that, excluding countries that could have potentially contributed to the setting of the German prices, the triple difference estimator is almost not affected. Both the preferred model in Column 2 and the model in Column 4 present a not significant coefficient for the variable $lnPREV$, a positive and significant value for the natural logarithm of the GDP per capita,

and a negative and significant effect of product's obsolescence. All three are in fact in line with existing empirical evidence.

Table 1.3 shows in Columns 1 and 2 the results of the models excluding products launched in countries that explicitly refer to Germany in their domestic ERP criteria. Moreover, Columns 3 and 4 of Table 1.3 reports the estimates of the models with only observations of products launched in countries that do not rely on any ERP criteria at all in their pharmaceutical price regulations. Overall, the results in Table 1.3 are intended to rule out the possibility

Table 1.3: Effect of AMNOG on German prices/2

	No GER in ERP set		*No ERP*	
Dep. Var.: Ln Price	(1)	(2)	(3)	(4)
Ger × Post × Reg	-0.119*	-0.243***	-0.162***	-0.207***
	(0.063)	(0.067)	(0.059)	(0.064)
Ger × Post	-0.097*	0.022	-0.076	-0.031
	(0.051)	(0.056)	(0.051)	(0.054)
Ger × Reg	-0.066*	0.033	-0.086**	-0.045
	(0.035)	(0.035)	(0.037)	(0.037)
Post × Reg	-0.034	-0.016	-0.005	0.009
	(0.045)	(0.037)	(0.032)	(0.027)
Ln prev		0.003		0.037
		(0.076)		(0.096)
Ln GDP p.c.		-3.197***		-1.083**
		(0.566)		(0.535)
Prod Age		-0.007		0.001
		(0.008)		(0.007)
Constant	1.139***	35.557***	1.237***	12.512**
	(0.029)	(6.513)	(0.043)	(6.207)
Prod, Year, Country FE	Yes	Yes	Yes	Yes
Observations	4131	4131	3778	3778
R^2 adj.	0.990	0.990	0.994	0.994

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

that control observations are affected by the AMNOG-regulated prices, so that the results outlined in Table 1.2 would be underestimated. The coefficients associated with the triple interaction terms of models that include covariates (Columns 2 and 4) are greater in absolute value with respect to the coefficient associated with the model with all observations (-0.243 and -0.207), suggesting a possible underestimation of the true effect—possibly due to the ERP cross-referencing mechanism.

In general, the results reported in Table 1.2 and Table 1.3 can be interpreted as a price reduction of German prices due to the negotiation process introduced with the AMNOG reform in 2011, with -16.4% as the—rather conservative—preferred point estimate. The

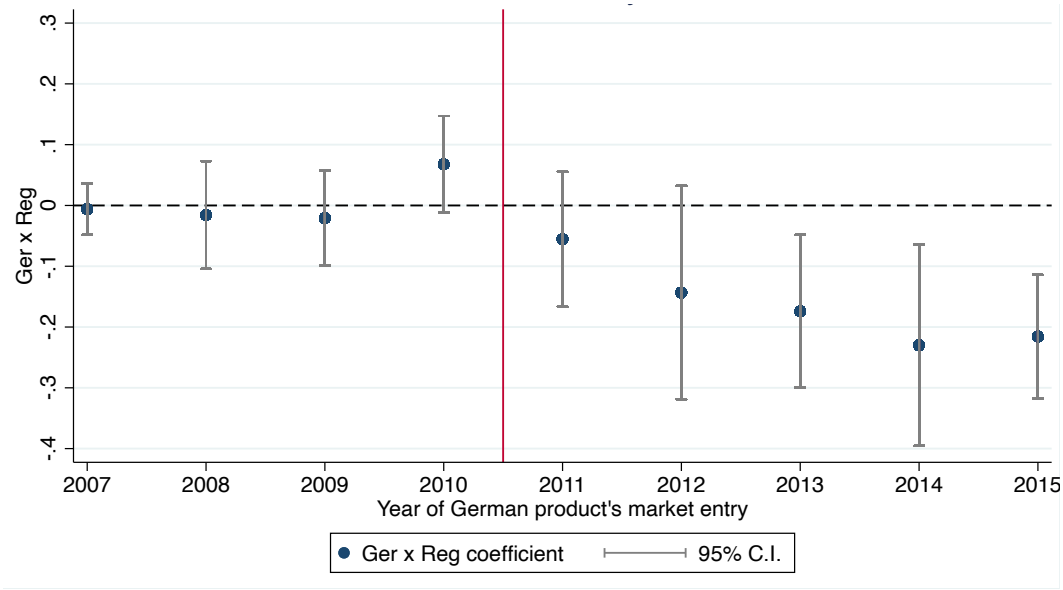
main results shown in Table 1.2 are robust to the exclusion of products launched during the year 2011 (Table A.1.3 in the Appendix). In fact, this transitional period could have been characterized by uncertainty over the correct submission of the dossiers by manufacturers (Lauenroth and Stargardt, 2017). The results are also robust to in-time placebo test (Table A.1.4 in the Appendix) and to leave-one-out analysis (Tables A.1.5 to A.1.8 in the Appendix). Moreover, the two "intermediate" difference-in-differences in Table A.1.9 for Germany and for control countries show that the effect is entirely driven by AMNOG reform in Germany, whereas products in control countries do not experience any price variation over time, whether they are launched before or after 2011. Finally, I control for the fact that the number of observations that fall under my definition of "regulated" is generally greater than the number of "unregulated" observations (Table A.1.10 in the Appendix). Specifically, the farther in time products entered the market, the greater the difference between the number of unregulated and regulated observations and, since product prices are expected to decrease over time, regulated observations of pre-2011 products could be disproportionally more affected by this price dynamic. Thus, the regulated-unregulated comparison for pre-2011 might be overestimated in absolute values, leading to an underestimation of the triple difference results. Table A.1.10 in the Appendix shows that the results are still in line with the baseline analysis.

Figure 1.2 below shows an event study reporting the coefficient of the interaction term $Ger_c \times Reg_{it}$ (with the indication of the 95% confidence intervals) from an OLS model with the log price as the dependent variable, analog to that in Column 2 of Table 1.2, but stratified for each group of products depending on the year of market entry in Germany (on the x-axis). In other words, Figure 1.2 shows the effect of the reform on regulated German prices with respect to unregulated German prices (as defined in Section 1.3), as compared to the same difference for controls for each year of products' market entry. The results suggest that the effect on regulated German prices becomes significant for products that entered the German market after the year 2013, although a not significant declining trend is still observable for the years 2011 and 2012. This is coherent with the expectation that, during this transitional period, the negotiation process might not have worked perfectly.[18]

Figure 1.3 takes a different approach and reports the price variation between German and control products at each product's life cycle stage. In particular, each product's market entry is normalized to occur at $t=0$. Then, multiple OLS regressions are performed, one for each quarter of the product's life cycle (in months on the x-axis), with the log price as the dependent variable, $Ger_c \times Post_t$ as the interaction term of interest, the usual covariates, and

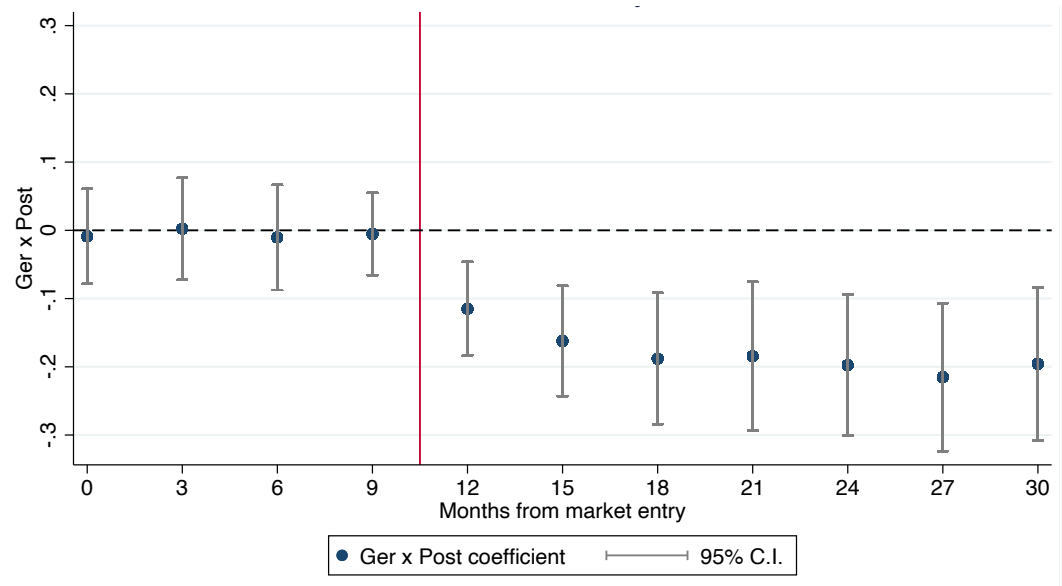
[18] More precisely, manufacturers were advised on the completeness of their dossiers by the G-BA and granted an additional 3 months to complete them if deemed incomplete (Lauenroth and Stargardt, 2017).

Figure 1.2: Event study (in years)



with product and country fixed effects. Figure 1.3 shows a significant and persistent effect on

Figure 1.3: Product's life cycle (in months)



German prices of those products launched after 2011, limited to the 12^{th} months since the first observation. This is in accordance with the negotiation process introduced by AMNOG. Moreover, this is robust to the one-by-one exclusion of control countries.

1.5.1 Opportunistic Behavior of the Manufacturer

In this section, I consider the possibility that the results reported in the previous section are due to the *opportunistic behavior* of the manufacturer, defined as the action of setting higher entry prices in response to the reform to compensate for the possibility that it leads to price reductions after the negotiation is completed. I test this hypothesis with the model shown in Equation 1.2. Unregulated prices satisfy the condition $Reg_{it}=0$: those prices observed for the first year after the market entry, launched before or after 2011.

$$\begin{aligned} y_{ict}(Reg_{it}=0) =& \beta_0 + \beta_2 Ger_c + \beta_3 Post_t + \\ &+ \beta_4 (Ger_c \times Post_t) + \beta_5 \mathbf{X}_{ct} + \theta_i + \delta_t + \gamma_c + \varepsilon_{ict} \end{aligned} \tag{1.2}$$

In the presence of opportunistic behavior by the manufacturer, the coefficient of the interaction term $Ger_c \times Post_t$ would be positive, suggesting that the results shown in Table 1.2 could be overestimated. If, on the other side, manufacturers have not changed how they set prices after the reform, I should not find any significant effect. Table 1.4 shows, in Column 1, the fixed effect DiD model limited to unregulated observations—those that fulfill the condition $Reg_{it}=0$. Coherent with Figure 1.3, the coefficient of the interaction $Ger_c \times Post_t$ in Column 1

Table 1.4: Opportunistic behavior of the manufacturer

Dep. Var.: Ln Price	*unregulated*	*regulated*
Ger × Post	-0.030	-0.185***
	(0.032)	(0.047)
Post=1	-0.031	-0.007
	(0.045)	(0.022)
Ln prev	-0.034	0.005
	(0.022)	(0.026)
ln GDP pc	0.090	0.255***
	(0.109)	(0.066)
Years since first launch	-0.021**	-0.014***
	(0.010)	(0.004)
Constant	0.703	-1.763**
	(1.206)	(0.788)
Product, Year, Country FE	Yes	Yes
Observations	4019	11105
R^2 adj.	0.995	0.995

Robust standard errors clustered at the product level in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Column (1): obs. limited to $Reg = 0$. Column 2: obs. limited to $Reg = 1$.

is negative and not significant, and thus it fails to provide evidence of variations in unregulated

prices after the reform. Nevertheless, the lack of a significant result can be explained by imprecision due to the smaller number of observations—although it is reassuring that the sign is opposite to what was expected had the opportunistic behavior occurred. For this reason, the coefficient might be cautiously interpreted as equal to zero. This is in line with what is found in Lauenroth et al. (2020), who also report no evidence of opportunistic behavior. Column 2 of Table 1.4 shows, as a placebo, the analysis for regulated prices only (that is, conditional on $Reg_{it}=1$). The interaction term's coefficient is significant and equal to -0.185, and it confirms the strong, negative, and significant effect associated with the AMNOG reform (Table 1.2). Both Columns 1 and 2 are robust to the exclusion of observations of the year 2011.

1.6 Discussion and Conclusions

In 2011, Germany introduced a new HTA procedure, the new Act to Reorganize the Pharmaceuticals Market (AMNOG), 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: *i)* the price of the closest comparator; *ii)* the added therapeutic value with respect to the closest comparator, and *iii)* the EU price level of the product.

The present paper investigates the effect of AMNOG on pharmaceutical prices by employing a triple difference method. This approach allows the exploitation of the specific features of the negotiation process prescribed by the AMNOG legislation, confirming the successful introduction of the HTA reform in Germany. In fact, I show that the causal impact of the reform on the prices of cancer medicines amounted to a price reduction of about 16.4%. The effect is smaller in magnitude than the raw comparison between "regulated" and "unregulated" German prices after the reform because it likely accounts for the downward price trend of pharmaceuticals that would have been experienced by German products even in the absence of the reform. I checked for what I defined as a form of opportunistic behavior of manufacturers on German entry prices, which could bias the estimates. In fact, during the free-price window of 12 months ensured by the AMNOG legislation, manufacturers might have set higher prices to counteract the expected negative impact of AMNOG's negotiation process on revenues. I find no evidence of this opportunistic behavior.

A possible limitation of these results could be the presence of confidential discounts and rebates, which are not (and cannot be) included in the list price per milligram of active substance—since only mandatory discounts can be considered. In general, the face value

of medicines bears limited resemblance to what payers actually pay (Morgan et al., 2017). Germany adopts a mandatory scheme of discounts and the German legislation does not suggest any possible hint of the systematic application of hidden agreements outside the "official" mandatory framework.[19]

Secondly, I considered only the price dimension of the HTA reform: however, a change in HTA regulation can lead to substantial delays in the adoption of products in domestic and neighbour countries, and it has been confirmed, for the German case, by the recent work of Büssgen and Stargardt (2022). A possible stream for future research can link those two dimensions (temporal and price dimensions) in order to have the full picture of the impact of AMNOG. Moreover, it would be of particular interest to explore the cross-country interaction among different pharmaceutical regulations, and the role of AMNOG in it, especially regarding possible spillover effects on other countries and the associated mechanisms.

[19] This is also in line with what has been suggested by personal communication with experts and professionals.

Chapter 2

ERP with Discounts: Does It Pay to Keep a Secret?

G. Righetti

Abstract *External reference pricing (ERP) is a policy tool widely used among EU Members to curb pharmaceutical spending, whereby national regulators link price negotiations for a new medicine to international prices for the same product. Its wide adoption can negatively impact the pharmaceutical industry if low list prices propagate due to cross-referencing. To circumvent it, manufacturers can either delay the launch of new medicines in low-income markets or concede secret discounts on list prices. Although the former channel is well established, the evidence on the latter remains anecdotal, despite the growing public pressure advocating for more transparency. The present paper delves into this ongoing debate. I set a model with two countries, Home and Foreign, and a Manufacturer. Home adopts ERP by referring to the Foreign price, when available, and the Manufacturer sets the price in the two markets, the launch sequence of new drugs, and the secret discount on the Foreign list price. I show that, although the Home country would disproportionately benefit from such bans at the expense of the Manufacturer and the Foreign country, total Welfare would ultimately increase with a fully transparent ERP scheme.*

Keywords Pharmaceutical regulation, ERP, secret discount, launch delay

JEL codes I18, L51, F10

2.1 Introduction

Numerous efforts have been put in place among European countries to reduce the disproportionate expansion of pharmaceutical expenditure. In fact, although marketing authorization of medicines has been harmonized under the European Medicine Agency (EMA), pricing and reimbursement decisions remain the responsibility of Member States, conditional on compliance with the EU Transparency Directive.[1] One of the main paths followed by European Regulators is represented by the reliance on external reference pricing (ERP) (Espin et al., 2014; Rémuzat et al., 2015). ERP is the practice of using the price of new medicines in one or several countries (called "reference countries") to derive a reference price, which is used in setting or negotiating the price of the product (WHO, 2013). The criteria for the selection of the appropriate countries to be included in the "reference basket" range from geographical proximity to income per capita or market size (Espin et al., 2014; WHO, 2020b). ERP regulations have the common aim of ensuring that countries do not overpay for new medicines with respect to their neighbors, and, in general, they have proven successful (Kanavos et al., 2020). As of 2020, a form of ERP is adopted in the majority of European countries (with the exceptions of Sweden and the UK), as well as in high- and middle-income countries of other regions, such as Brazil, Egypt, Saudi Arabia, Thailand, Turkey, the United Arab Emirates. Moreover, the US is also considering the implementation of some form of external reference pricing (Frank et al., 2022).[2] Calculation methods to derive the benchmark price vary substantially: the majority refers to the average price of the ERP basket; other countries to the minimum price (Bulgaria, Hungary, Poland, Romania, Slovenia, Spain, Russia and Turkey, among others) or to the average of the lowest prices (Czech Republic, Greece, Norway, Slovakia) (WHO, 2020b).[3]

If all countries strictly applied ERP—the so-called "regulatory convergence" predicted by Birg (2016)—there should be a trend toward uniform pricing for pharmaceuticals (Stargardt and Schreyögg, 2006; Toumi et al., 2014; Vogler et al., 2020). In fact, as put by Geng and Saggi (2017), a regulator's ERP policy is, from the firm's perspective, a constraint on the degree of international price discrimination that can be practiced. The evidence confirms a downward price convergence over time (Csanádi et al., 2018; Leopold et al., 2012), which is generally believed to jeopardize pharmaceutical industry profits (Danzon, 1997). To circumvent the

[1] Council Directive 89/105/EEC (21 December 1988) on the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

[2] To a large extent, ERP can be regarded as an international Most Favored Customer Clause (MFCC) under discussion in the US. As a matter of fact, the Medicaid program in the US has a "most-favored customer" procurement rule that, along with its rebate program, creates cross-market externalities with the commercial market (Feng et al., 2023), similarly to ERP.

[3] For a detailed overview, see WHO (2020b) guidelines.

negative impact of ERP, manufacturers can choose to avoid *tout court* the launch in certain countries (Birg, 2016; Houy and Jelovac, 2015). Indeed, there is evidence of strategic launch delays of new medicines in countries with more stringent regulations (Cockburn et al., 2016; Danzon et al., 2005; Heuer et al., 2007; Kyle, 2007), or in low-income countries (Danzon and Epstein, 2008; Lanjouw, 2005).[4] In particular, Maini and Pammolli (2023) reported entry delays of up to one year in eight low-income European countries in response to ERP. Another consequence of the wide adoption of ERP schemes is the general price increase in reference countries (Ackermann, 2010; Birg, 2016; Geng and Saggi, 2017; Mariñoso et al., 2011), which has been observed in the EU in the empirical analysis of Chapter 3 and for which there is structural evidence for the case of Canada, had the US referenced Canadian pharmaceutical prices (Dubois et al., 2022).

The inclusion of a country in the ERP basket of another creates the incentive for manufacturers to seal confidential agreements with the reference country. Such agreements are ultimately designed to retain—or to partially restore—the ability to price discriminate while preventing the propagation of low list prices across markets (Danzon and Towse, 2003). In fact, the presence of confidential agreements (or managed entry agreements, MEA) creates the distinction between the public price tag of the product (list price) and what is actually paid (net price). Examples of MEA can be secret discounts, supply contracts, risk-sharing agreements, patient access schemes, product listing agreements, and others (Ferrario and Kanavos, 2013; Vogler et al., 2012). Indeed, both the evidence on the price convergence and the price increase in the reference countries are limited to *list* prices, but not to prices net of discounts (Barrenho and Lopert, 2022; Danzon and Towse, 2003; Vogler et al., 2020). The tendency to concede confidential agreements to national regulators has increased over time (Shaw and Mestre-Ferrandiz, 2020)—possibly due to the wide use of ERP across countries (Persson and Jönsson, 2016). Such discounts have been reported in 22 European countries out of the 32 that were surveyed by Vogler et al. (2015), and range between 40% and 70% for specialty pharmaceuticals and from 10% to 50% for primary care drugs (Morgan et al., 2017).[5] In general, confidential agreements can be regarded as one of the most promising paths towards (indirect) differential pricing (Danzon, 2018; Danzon and Towse, 2003)—which, in turn, is more efficient than uniform pricing.[6] The general wisdom of the pharmaceutical industry is that a restored ability to price discriminate would favor product entry in low-income countries.

[4] A complementary point of view is provided by Lakdawalla (2018), who notices that it would require very aggressive referencing to drive gross margins below zero and justify launch delays. He argues that this might be suggestive of manufacturers signaling to other countries that adopting tighter reference-pricing schemes will result in failure to launch or delays in launch.

[5] These findings are confirmed by a 2021 EURIPID survey (Russo et al., 2021).

[6] This argument can be traced back to Ramsey (1927).

However, affordable access to medicines for Central and Eastern Europe countries has not, in fact, improved (Vogler and Paterson, 2017). One of the reasons might be that, rather than the ability to pay, secret discounts are capturing the ability to negotiate, thus favoring the monopsony power of high-income countries over "smaller" national payers (Kaló et al., 2013; Morgan et al., 2020). Incidentally, confidential agreements not only represent a threat to the relevance of ERP schemes, but they can also "[...] *prevent the general public from scrutinizing public expenditure, and undermine the accountability of reimbursement and coverage decisions*" (Barrenho and Lopert, 2022).

Public pressure for greater transparency resulted in the 2019 World Health Assembly resolution, where a significant number of national regulators have stepped forward to "*take appropriate measures to publicly share information on the net prices of health products*" and to "[share] *the amount received by manufacturers after subtraction of all rebates, discounts, and other incentives*", arguing that the publication of price net of confidential discounts will favor competitive prices (WHA, 2019).[7] Recent evidence by Grennan and Swanson (2020) points in this direction, showing that, in the context of hospitals' stent acquisition, information on peer acquisition prices can indeed lead to lower prices. Contextual with the need to share the net prices of pharmaceuticals, voluntary cross-country collaborations have emerged over time, such as the Baltic Procurement Initiative, Beneluxa Initiative, Fair and Affordable Pricing, Nordic Pharmaceutical Forum and Valletta Declaration (WHO, 2020a).[8] Notably, in 2018 the members of the Beneluxa Initiative successfully concluded a negotiation with Biogen on the reimbursement of Spinraza® (nusinersen).[9]

Paradoxically, Riccaboni et al. (2022) shows that economically rational low- and middle-income countries should instead oppose such resolutions since they are expected to be harmed by more transparency. However, the evidence on the effectiveness of an increase in price transparency is still scarce and ambiguous (Barrenho and Lopert, 2022): for instance, Gamba

[7] The resolution was put forward by Andorra, Brazil, Egypt, Eswatini, Greece, India, Italy, Kenya, Luxembourg, Malaysia, Malta, Portugal, Russia, Serbia, Slovenia, South Africa, Spain, Sri Lanka and Uganda. https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_ACONF2Rev1-en.pdf (accessed 23 January 2024).

[8] The Baltic Procurement Initiative was established in May 2012 and comprises Estonia, Latvia and Lithuania. It performs joint procurement of vaccines. The Beneluxa Initiative was established by Belgium and the Netherlands in 2015 and extended when Luxembourg (2015), Austria (2016) and Ireland (2018) joined. Members collaborates over HTA, pricing, reimbursement negotiations and information sharing. The Fair and Affordable Pricing (FAAP) initiative was signed in 2017 and it comprises Czechia, Hungary, Poland and Slovakia. It aims to perform joint HTA reports and price negotiations. The Nordic Pharmaceutical Forum includes Denmark, Norway, Sweden and Iceland, with Finland as an observer. It aims to increase purchasing power to perform joint procurement for older and new (primarily hospital) medicines. The Valletta Declaration consists of 10 countries in southern and eastern Europe (Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Slovenia and Croatia) that aim to work together on horizon scanning, HTA and price negotiations (WHO, 2020a).

[9] Beneluxa press release available at: https://beneluxa.org/news1

et al. (2020) show how the introduction of a MEA analogous to secret discount leads to a list price increase. In this respect, the theoretical work by Cabau and Gordon (2022), which is also the most similar to the present analysis, is an exception. Their model rationalizes ERP as a response to an information asymmetry and secret rebates as a response to ERP itself. They conclude that, with secret rebates, manufacturers are able to avoid price interdependencies across markets. At the same time, reference countries would be able to tailor their willingness to pay in negotiations based on the information disclosed. However, differently from the present analysis, they look at the price signal coming from the country that first negotiates with the Manufacturer, which influences the negotiation process of the ERP adopter that negotiates after. Instead, I do not take the entry order between the ERP adopter and reference country as exogenous; rather, it is the result of the incentives of the Manufacturer. Moreover, I explicitly consider the ERP regulation to be the trigger for the price of the ERP adopter, assuming the latter is allowed to revise its price based on its ERP price ceiling. In my view, this is the most prevalent form of spillover caused by ERP regulation that may involve the use of secret discounts.[10]

I explore the economic incentives of introducing secret discounts on list prices of pharmaceuticals in the ERP context. I set a two-country model (Home and Foreign) where a Manufacturer produces and sells a patent-protected product, sets the launch schedule in the two markets, and is allowed to concede a discount on the list price of the Foreign market. The key element is that the discount conceded by the Manufacturer to the Foreign country is hidden from the Home country, which only observes list prices. Therefore, if the Home health authority adopts ERP, it can only use the Foreign list prices as its price ceiling. I show that, in the presence of ERP, the Manufacturer has the incentive to concede a secret discount and, under certain conditions, to delay the entry into the reference country. A ban on confidential agreements would increase the price paid by the reference country as well as the associated product's entry delay, but it can ultimately increase total welfare. Finally, the Home country would disproportionately benefit from such bans at the expense of the Manufacturer and the Foreign country.

This paper belongs to two strands of literature. First, it contributes to the theoretical work on the impact of the adoption of ERP. However, differently from Garcia Mariñoso et al. (2011) and Geng and Saggi (2017), it incorporates the dynamic setting of the launching decisions of

[10] In other words, they consider the effect of ERP (and of the rebates that are optimally chosen because of it) as those arising *from* the reference country negotiation process *to* the ERP adopter that tailors its price negotiation, while my setting considers the effect of ERP coming *from* the ERP adopter decision to include the reference country, *to* the price-setting process in the reference country that adjusts to the ERP policy adopted abroad.

the Manufacturer, in the spirit of Houy and Jelovac (2015). Moreover, similar to Cabau and Gordon (2022), I introduce the confidentiality issue in the ERP framework. Finally, from a policy perspective, this work contributes to the debate over price transparency, whose impact is not yet well understood (Barrenho and Lopert, 2022, and references therein).

The remainder of the work is organized as follows. Section 2.2 proposes the theoretical framework of ERP adoption with secret discounts. Section 2.3 presents the results. Finally, Section 2.4 discusses the findings and concludes the work.

2.2 Model of ERP with Secret Discounts

I consider a model with three agents: the health authorities of the Home country (H) and of the Foreign country (F), and the Manufacturer (M) of a patent-protected pharmaceutical product, serving both markets. M maximizes the profit made by selling the product in H and F throughout the patent protection for that product, which is assumed to last in the continuous interval $t \in [0, 1]$, where $t = 0$ corresponds to market authorization and $t = 1$ to the expiration of the patent. For the sake of simplicity and without loss of generality, I assume that profits fall to zero after the patent protection expires,[11] that the marginal cost of producing the drug is negligible, and that the R&D cost is sunk. The health authority in country H adopts ERP regulation by explicitly enforcing the price set in F as its price ceiling.[12] This will be the only form of price regulation in this model, to abstract from any other incentives. An extension is explored in Section **??** where the health authorities are allowed to price negotiate with the Manufacturer in the standard Nash bargaining framework. I assume that M does not face the threat of parallel trade for products sold in H and F.[13] Most importantly, as the price ceiling becomes binding, H will promptly adjust its price. This simplifying assumption is somewhat in line with the fact that ERP regulations usually prescribe price revision based on the ERP benchmark price, although the frequency can be heterogeneous (Espin et al., 2014). Nevertheless, relaxing this assumption does not affect the results. Finally, the ERP policy is not retroactive: as soon as the price in the foreign country is available, H's ERP regulation will impose the price cap from that point in time.

[11] Although it might not be entirely true empirically, this simplifying assumption reflects the fact that after patent protection the Firm generally faces some degree of competition which might affect the pricing strategy, along with profit itself.

[12] A strict price cap rule can be regarded as a proxy for ERP regulations in general, although ERP is often one of the many criteria in the price-setting mechanism of the national regulators. See also WHO (2020b).

[13] Parallel trade is a form of arbitrage that exists when there are significant price differences between countries: goods that are produced under the protection of a patent are placed into circulation in one market and then imported into a second market without the authorization of the owner of the intellectual property right (IPR). The EU provides for regional exhaustion of IPR, thus allowing parallel trade within the EU trading bloc, but it bans it from non-member countries.

The demand functions in countries H and F are $Q_H = 1 - p_H$ and $Q_F = (v - p_F)K$, respectively. The negative slope of these functions reflects the fact that the marginal benefit varies across patients, depending on individual characteristics. Since it is assumed that the price of the product is fully reimbursed by each regulator and that patients in each country do not face any copayment, given the price, the quantity is assumed to be determined by the payer. In practice, payers do so by defining eligibility criteria of patients for whom the cost is reimbursed. In the demand function of F, v and K are scaling factors, respectively of willingness to pay and market size, which allow us to account for heterogeneity across countries.

M chooses simultaneously the Home price (p_H), the Foreign price (p_F), the launch schedule (d_H, d_F), and the secret discount conceded to F (μ).[14] The launch schedule defines two points in time at which M decides to serve each market under patent protection, d_H and d_F, with $d_H, d_F \in [0, 1]$. However, if H is the ERP adopter and the ERP price ceiling is binding for H, there is no incentive to launch the product first in F and then in H.

Proof. H adopts a form of ERP by referring to the price set in F, and the price in F is binding for H. Consider the following profit maximization problem: $\max_{d_H} \Pi \equiv \int_{d_H}^{d_F} \pi_H(p_H)dt + \int_{d_F}^{1} \pi_H(p_F)\, dt + \int_{d_F}^{1} \pi_F(p_F, \mu)\, dt - \psi(\mu) - \phi_1(d_H) - \phi_2(d_F)$, where $\psi(\mu)$, $\phi_1(d_H)$ and $\phi_2(d_F)$ are the cost to concede the secret discount, to delay the entry in the Home market and to delay the entry in the Foreign market, respectively. It is straightforward to show that the solution of the maximization problem with respect to d_H is equal to zero. □

Therefore, the entry delay in the Home market can be normalized to $d_H = 0$ and I can refer to the launch schedule (d_H, d_F) as simply $d_F = d$, which also defines the point in time when ERP is triggered in H through the binding price ceiling.[15]

The secret discount μ is the key element in this model. I denote it as the percentage discount on the list price that is conceded by M to F, so that $0 \leqslant \mu \leqslant 1$. The introduction of the discount raises the need for a distinction, limited to the Foreign market for parsimony, between the *list price* p_F and the *price net of discount* (or *net price*), which can be expressed as $\tilde{p}_F = (1 - \mu)p_F$.

Lemma 1. *Since H cannot observe the secret discount μ, the price ceiling in the presence of discount is the publicly available list price p_F, while F would pay the net price $\tilde{p}_F$.*

Notice that the type of secret discount that falls under the scope of the present analysis is explicitly associated with the adoption of ERP by the Home country. That leads to the

[14] I rely on Lakdawalla (2018) on the simultaneity between pricing and launching strategy of manufacturers.
[15] Hereafter, the cost of delay simply refers to the launch in the Foreign market.

following Remark.

Remark. *The secret discount considered in the present analysis is only the discount strategically conceded to the Foreign country to indirectly affect Home list prices.*

The Remark above implies that other types of discount might be conceded, either in H or in F, regardless of the introduction of ERP. However, they remain beyond the scope of the present analysis. Both delays and discounts are associated with a cost borne by M.

Lemma 2. *The entry delay in the Foreign market and the secret discount conceded to the Foreign regulator come at a quadratic cost $\phi(d) = cd^2/2$ and $\psi(\mu) = b\mu^2/2$, respectively.*

The cost for the discount derives from the effort of keeping the price hidden from H, which is increasing in the magnitude of the discount—the larger the discount, the more difficult is to keep it secret from H. Moreover, one should expect that the marginal cost of the discount is increasing with its magnitude: this is to reflect that it is increasingly more difficult to keep the discount hidden from the public. Similarly, the cost for the delay can be regarded as the public pressure arising from the fact that M is not providing an innovative and potentially life-saving drug. This pressure can be interpreted as reputation cost, and it behaves in the same way as the cost associated with the secret discount.[16]

As a starting point, I outline the equilibrium when H does not commit to any ERP pricing regulation, and therefore (as for the above Remark), no secret discount is conceded. As it is standard in the literature, I assume that agents do not discount time. I denote the equilibrium as "Segmented" since the two markets, in the absence of ERP, are not interdependent. In that case, M maximizes its profit Π as follows.

$$\max_{p_H,\, p_F,\, d} \Pi^S \equiv \int_0^1 \pi_H(p_H)dt + \int_d^1 \pi_F(p_F)dt - \phi(d) \tag{2.1}$$

Where $\pi_H = p_H Q_H(p_H) = p_H(1-p_H)$ and $\pi_F = p_F Q_F(p_F) = p_F(v-p_F)K$. The solution corresponds to third-degree price discrimination: the prices that maximize M's profit are those of the monopolist that is capable of segmenting the two markets, $p_H^S = 1/2$ and $p_F^S = v/2$. Quite intuitively, there is no incentive to postpone the launch in F, so that $d^S = 0$. The optimal profit is $\Pi^S = (1+v^2K)/4$. Finally, notice that for $v \leqslant 1$ we have that $p_F^S \leqslant p_H^S$ and for $v > 1$ we have that $p_F^S > p_H^S$. The Surpluses of the two countries are calculated as follows:

$$S_H^S = \frac{1}{2}\int_0^1 \left(1-p_H^S\right)^2 dt \quad \text{and} \quad S_F^S = \frac{1}{2}\int_{d^S}^1 \left(v-p_F^S\right)^2 K dt \tag{2.2}$$

[16] Alternatively, the cost of delay can also be interpreted as a form of discounting, although not explicitly present in this model.

Total Welfare is denoted simply as the sum of Profit, Home Surplus and Foreign Surplus:

$$W \equiv \Pi + S_H + S_F \tag{2.3}$$

Therefore, under Market Segmentation we would have $S_H^S = 1/8$, $S_F^S = v^2K/8$ and $W = \frac{3(1+v^2K)}{8}$. As expected, S_F^S and W are increasing in both v and K, while S_H^S is constant as it does not depend on parameters associated to F.

In what follows, I explore in Section 2.2.1 the benchmark model of ERP, or "Transparent ERP", and in Section 2.2.2, I propose a model of ERP that allows for the presence of a secret discount conceded to F by M, or "Opaque ERP".

2.2.1 Transparent ERP

This section draws from the ERP model of Geng and Saggi (2017) but it adds the dynamic setting, in the spirit of Houy and Jelovac (2015). If H introduces the ERP regulation, it commits to adopt the price set in F as the price ceiling, as soon as it becomes available at time d. The profit to be maximized is shown in Equation 2.4.

$$\begin{gathered}\max_{p_H,\, p_F,\, d} \Pi^T \equiv \int_0^d \pi_H(p_H)dt + \int_d^1 \pi_H(p_H, p_F)dt + \int_d^1 \pi_F(p_F)dt - \phi(d) \\ \text{s.t.:} \quad p_H \leqslant 1 \text{ and } p_F \leqslant v\end{gathered} \tag{2.4}$$

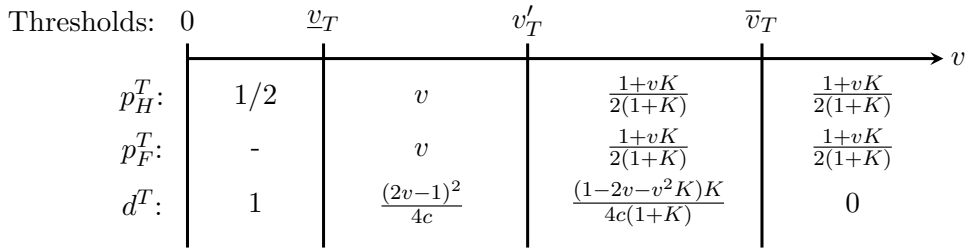
Where $\pi_H(p_H, p_F) = \min\{p_H, p_F\}(1 - \min\{p_H, p_F\})$. The first two sums of Equation 2.4 represent the profit in the Home market from 0 to d and from d to the expiration of the patent protection, respectively, while the third term is the profit in the Foreign market from product entry at d to patent expiration, as in Equation 2.1. The time that spans from d to the patent expiration defines the period under which the ERP in H is enforced. The constraints $p_H < 1$ and $p_F < v$ prevent M from having negative quantities sold in each markets. The optimal prices and the optimal delay under the Transparent ERP, denoted with the superscript T, are:

$$p_H^T = \begin{cases} 1/2 & \text{if} \quad v \leqslant \underline{v}_T \\ p_F^T & \text{if} \quad \underline{v}_T < v \leqslant 1 \end{cases} \quad \text{and} \quad p_F^T = \begin{cases} v & \text{if} \quad \underline{v}_T < v \leqslant v'_T \\ \frac{1+vK}{2(1+K)} & \text{if} \quad v'_T < v \leqslant 1 \end{cases} \tag{2.5}$$

$$d^T = \begin{cases} 1 & \text{if} \quad v \leqslant \underline{v}_T \\ \frac{(2v-1)^2}{4c} & \text{if} \quad \underline{v}_T < v < v'_T \\ \frac{(1-v^2K-2v)K}{4c(1+K)} & \text{if} \quad v'_T < v < \overline{v}_T \\ 0 & \text{if} \quad \overline{v}_T \leqslant v \end{cases} \tag{2.6}$$

The results in Equations 2.5 and 2.6 define three threshold values for v: $\underline{v}_T$, v'_T and $\overline{v}_T$. The results are summarized in Figure 2.1, depending on the level of v with respect to these thresholds.

Figure 2.1: Optimized variables under Transparent ERP



Where $\underline{v}_T = 1/2 - \sqrt{c}$ is the value of v for which M is indifferent between entering in both markets at a uniform price $p_F^T = p_H^T = v$ with a delay equal to $d^T = \frac{(2v-1)^2}{4c}$ and not entering in F—thus, with a delay equal to 1—while serving the Home market at $p_H^T = 1/2$.[17] For this reason, $\underline{v}_T$ can also be denoted as the "no-launch threshold" for v. Above the no-launch threshold, in the interval $\underline{v}_T < v < v'_T$ with $v'_T = \frac{1}{2+K}$, the product enters both markets at a price that matches the Foreign monetary benefit v, so that, in this interval, the quantity sold in the Foreign market is equal to zero and thus v'_T can be denoted as the "non-negative quantity threshold" for v.[18] As for the range $v'_T < v < \overline{v}_T$, instead, M still delays the launch in the Foreign market, but it sets a Foreign price that leads to a strictly positive quantity of the product being sold in F. Finally, the threshold $\overline{v}_T = \frac{\sqrt{1+K}-1}{K}$ defines the second corner solution for d^T, above which the optimal delay is equal to 0.[19] More precisely, it corresponds to the value of v above which M enters in H and F at the same time, so that $\overline{v}_T$ can be referred to as the "no-delay threshold" for v. Formally:

Proposition 2.1. *Under a model of Transparent ERP, there are two corner solutions for the optimal delay: $d^T = 1$ for $v \leqslant \underline{v}_T$ and $d^T = 0$ for $\overline{v}_T \leqslant v$. For intermediate values of v, the optimal delay has an interior solution that decreases with the cost parameter for the delay c, in F's market size K, and in the monetary equivalent v.*

Corollary 1 (Market entry under Transparent ERP)**.** *Under a model of Transparent ERP, one of the following occurs: i) for $v \leqslant \underline{v}_T$, the product does not enter the Foreign market; ii) for $\underline{v}_T < v < \overline{v}_T$ the product enters the Home and, with a positive delay, the Foreign market; iii) for $\overline{v}_T < v$ the product enters both the Home and the Foreign market with no delays.*

[17] More specifically, the value of v'_T is obtained by equating $\frac{(2v-1)^2}{4c}$ and 1 and solving with respect to v.
[18] This is calculated as the value of v such that $v'_T = \frac{1+vK}{2(1+K)}$.
[19] That is, the value obtained by solving $\frac{(1-v^2K-2v)K}{4c(1+K)} = 0$ with respect to v.

Corollary 2. *Under a model of Transparent ERP, for $\underline{v}_T < v < v'_T$ the Manufacturer prefers to "formally" enter the Foreign market with strictly positive delay but with zero quantity sold (and thus zero profit) to avoid part of the delay cost. Instead, for $v'_T < v < \overline{v}_T$ the Manufacturer still enters the Foreign market but at a price that allows a strictly positive quantity being sold in the Foreign market.*

Corollary 2 implies that, for certain values of v, the Manufacturer finds it optimal to enter the Foreign market with a quantity sold equal to zero, thus reducing in part the cost of the delay at the cost of triggering the ERP regulation in the Home market. This can be interpreted as an attempt by the firm to limit the cost of delaying the launch of the product into the Foreign market at the cost of triggering the uniform price through the ERP mechanism, even without making a profit in the Foreign market.

This is coherent with the fact that if the cost to delay the launch in F is equal to zero ($c=0$), the Manufacturer would face the standard *now-or-never* launching decision (Houy and Jelovac, 2015), which, however, is in contrast with the evidence that shows significant variability in the entry dates for the same product across countries, even net of any idiosyncratic component (Maini and Pammolli, 2023).

Corollary 3 (No cost of delay)**.** *In case the cost of delay is equal to zero, the Transparent regime will simply increase the range of values of v for which M does not enter the Foreign market including the interval $\underline{v}_T < v < \overline{v}_T$.*

The launch in the Foreign market, whether it is below or above the non-negative quantity threshold, occurs at a price p_F^T which triggers H's ERP regulation for $v \leqslant 1$—while it never does for $v>1$. When the ERP price ceiling is not triggered, there would be a scenario akin to the Segmented markets regime. Therefore, I can limit the scope of the analysis to the case where $v \leqslant 1$ (as it is in Figure 2.1) and leave aside the trivial case where $v>1$. It follows that:

Proposition 2.2 (Optimal prices under Transparent ERP)**.** *Under a model of Transparent ERP, the Foreign country always experiences a price increase, so that $p_F^T > p_F^S$ for any $v \leqslant 1$, with $p_F^T < p_H^S$ for any K.*

Proposition 2.2 is coherent with the literature on the optimal choice by H, which is always better off by adopting ERP as compared with no regulation, and with the fact that the equilibrium foreign price is higher than the firm's optimal monopoly price for that market (Geng and Saggi, 2017; Mariñoso et al., 2011). This implies that, whenever F is included in H ERP set, it should experience a price increase. This prediction is in line with the results of the empirical exercise in Chapter 3 and with Dubois et al. (2022). Moreover, the difference

between p_F^T and p_F^S is decreasing with K: the intuition is that the larger the market in the reference country, the less M needs to increase the Foreign price to recoup from the negative externality induced by the uniform price.

The optimal Home price p_H^T, Foreign price p_F^T and entry delay d^T identify the optimal Profit Π^T, Home Surplus S_H^T, Foreign Surplus S_F^T and total Welfare W^T. Under the Transparent ERP regime, the Home and Foreign surpluses are calculated as:

$$S_H^T = \frac{1}{2}\int_0^{d^T}\left(1-p_H^T\right)^2 dt + \frac{1}{2}\int_{d^T}^1\left(1-p_F^T\right)^2 dt \quad \text{and} \quad S_F^T = \frac{1}{2}\int_{d^T}^1\left(v-p_F^T\right)^2 K\,dt \tag{2.7}$$

The objects Π^T, S_H^T, S_F^T and W^T react differently to changes in the parameter v, depending on its level with respect to the thresholds for v (for the algebraic solution, see the Appendix A.2.1). In particular, for $v \leqslant \underline{v}_T$, since there is no entry in the Foreign market, they do not depend on the parameters associated with the Foreign market, v and K: Home surplus is constant and equal to 1/8, the Foreign surplus is equal to 0, and the Profit is decreasing in the cost of delay. Finally, the total Welfare, as the sum of the producer and consumer surpluses, also decreases with the cost of delay.

For values of v in the interval between $\underline{v}_T$ and v'_T, the optimal delay has an interior solution (Proposition 1), and thus M enters the Foreign market with a positive lag with respect to Home's entry. This creates an interdependence between the two markets through the ERP channel. Therefore, Π^T, S_H^T, S_F^T and W^T will depend on the Foreign market's parameter v, since it is the driver of the optimal uniform price. However, since the entry in the Foreign market is only formal and there is no quantity sold, the Foreign market size K does not play a role (Corollary 2). In this interval, the Home country receives the maximum possible level of surplus, since the ERP regulation becomes binding at the lowest possible value of p_F^T.

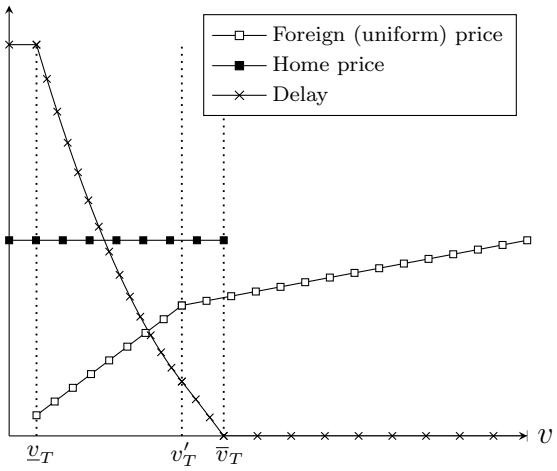
For values of v between v'_T and $\overline{v}_T$, the optimal delay still has an interior solution, but M enters the Foreign market with a price that can be afforded by the Foreign regulator—that is, the quantity sold is strictly positive. This creates the same interdependence between the two markets, not only through the parameter v but also through K. In particular, the optimal profit decreases in c and increases in v and K. Moreover, the Home surplus is increasing in v, K, and c. In this interval, the Foreign regulator benefits from the product's entry with a positive surplus, increasing in v, K, and in the cost of delay c. The total Welfare, for values of v that range between v'_T and $\overline{v}_T$, increases with v, K, and c. In fact, the direction of the impact of the delay on the consumer surpluses prevails over the impact on the Profit of the Manufacturer. The last relevant interval is for values of v between $\overline{v}_T$ and 1. Here, the delay does not play a role since the M finds it profitable to enter both markets simultaneously.

Therefore, all quantities do not depend on c, but they depend on F's market parameters v and K since the uniform price is still in force.

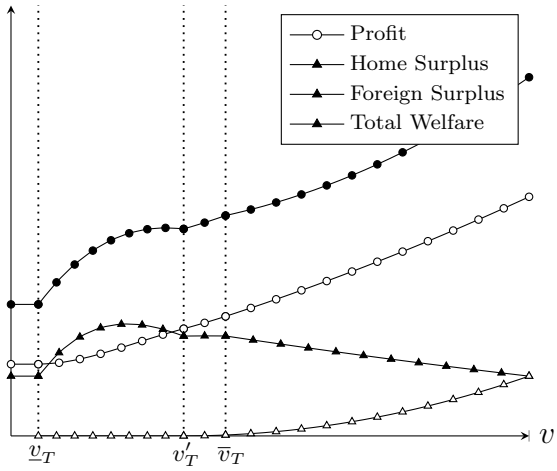
Figure 2.2a shows the optimal variables as a function of v as set by M under the Transparent ERP. Figure 2.2b shows optimal Profit, Home Surplus, Foreign Surplus, and Welfare under the Transparent ERP, as a function of v.

Figure 2.2: Optimized variables and Profit, Home and Foreign Surplus, and Total Welfare under Transparent ERP

(a) Optimal Variables ($K = 1$, $c = 0.2$)



(b) Π^T, S_H^T, S_F^T and W^T ($K = 1$, $c = 0.2$)



2.2.2 Opaque ERP

Under a more realistic scenario, denoted as "Opaque ERP", M is allowed to concede a discount on the Foreign price at a cost $\psi(\mu)$ (Lemma 2). The key feature of the discount is that it is kept hidden from H, which only observes (and, in case the ERP regulation is triggered, pays) the full list price p_F. M's incentive in setting the optimal discount is the following: since H can only use the list price set in F as the price cap due to its ERP commitment, M can inflate it to increase the (binding) price cap in the Home market and, at the same time, it is still able to set the optimal net price $\tilde{p}_F$ in the Foreign market through the optimal secret discount. In other words, the Manufacturer is able to restore its ability to price discriminate across the Home and the Foreign markets. The total cost of the secret discount is increasing with the level of μ at an increasing pace (Lemma 2). This is a reasonable assumption to the extent that the greater the magnitude of the discount, the more difficult it is for M to maintain confidentiality. Under the Opaque ERP regime, M maximizes the global profit with

respect to p_H, p_F, d, and μ as follows.

$$\max_{p_H,\, p_F,\, d,\, \mu} \Pi^O \equiv \int_0^d \pi_H(p_H)dt + \int_d^1 \pi_H(p_F)dt + \int_d^1 \pi_F(\tilde{p}_F, \mu)dt - \phi(d) - \psi(\mu) \quad \text{s.t.:} \quad p_H < 1 \text{ and } \tilde{p}_F < v \tag{2.8}$$

Where $\pi_F(p_F, \mu) = \tilde{p}_F\,(v - \tilde{p}_F)\,K$ is the profit made in F in the presence of the secret discount, and $\tilde{p}_F = (1-\mu)p_F$ is the price net of the discount. Again, the constraints of the maximization problem of Equation 2.8 are to prevent M from making a negative profit in each market. The non-negative profit constraint in the Foreign market depends on μ and is "looser" than the analog constraint under the Transparent regime since it is only required that the net price $\tilde{p}_F$, rather than the full list price, must be less than v. The first-order conditions (FOCs) of the profit maximization problem are the following, where the optimal values are indicated with the superscript "O":

$$\frac{\mathrm{d}\pi_H\left(p_H^O\right)}{\mathrm{d}p_H} = 0 \tag{2.9}$$

$$\frac{\partial \pi_F\left(p_F^O, \mu^O\right)}{\partial p_F} + \frac{\mathrm{d}\pi_H\left(p_F^O\right)}{\mathrm{d}p_F} = 0 \tag{2.10}$$

$$\pi_H\left(p_H^O\right) - \pi_H\left(p_F^O\right) - \pi_F\left(p_F^O, \mu^O\right) - \frac{\partial \phi\left(d^O\right)}{\partial d} = 0 \tag{2.11}$$

$$\frac{\partial \pi_F\left(p_F^O, \mu^O\right)}{\partial \mu} - \frac{\partial \psi\left(\mu^O\right)}{\partial \mu} = 0 \tag{2.12}$$

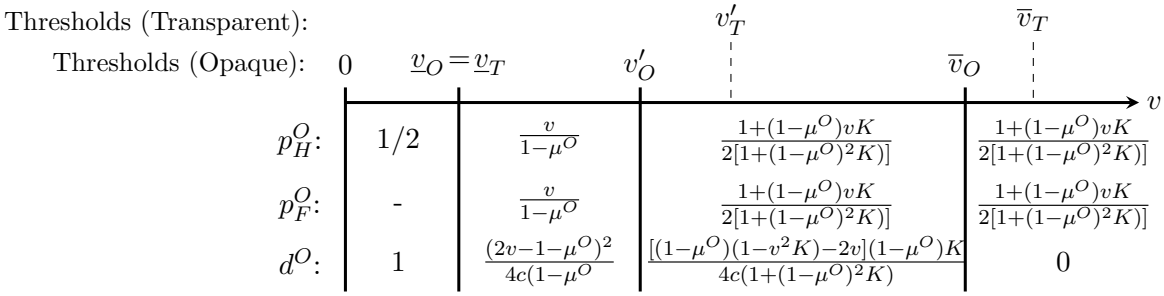
The first FOC (Equation 2.9) identifies the profit-maximizing price in the Home market. The second FOC (Equation 2.10) identifies the profit-maximizing uniform price in both markets when the ERP is triggered. The third FOC (Equation 2.11) equalizes the marginal benefit of a longer entry delay in the Foreign market, $\pi_H(p_H^O)$, with the marginal cost associated with it, $\pi_H(p_F^O)$, $\pi_F(p_F^O, \mu^O)$ and $\partial\phi(d^O)/\partial d$. Finally, the fourth FOC (Equation 2.12) equalizes the marginal benefit of a change in the secret discount with the marginal cost of hiding it. Specifically, the first two FOCs lead to the optimal price in the Home and Foreign markets, while the third FOC allows us to retrieve the optimal delay as a function of the discount.

$$p_H^O = \begin{cases} 1/2 & \text{if} \quad v \leqslant \underline{v}_O \\ p_F^O & \text{if} \quad \underline{v}_O < v \leqslant 1 \end{cases} \quad \text{and} \quad p_F^O = \begin{cases} \frac{v}{1-\mu^O} & \text{if} \quad \underline{v}_O < v \leqslant v'_O \\ \frac{1+(1-\mu^O)vK}{2[1+(1-\mu^O)^2K]} & \text{if} \quad v'_O < v \leqslant 1 \end{cases} \tag{2.13}$$

$$d^O = \begin{cases} 1 & \text{if} \quad v \leqslant \underline{v}_O \\ \frac{\left(2v-1-\mu^O\right)^2}{4c(1-\mu^O)^2} & \text{if} \quad \underline{v}_O < v \leqslant v'_O \\ \frac{\left[\left(1-\mu^O\right)\left(1-v^2K\right)-2v\right]\left(1-\mu^O\right)K}{4c\left(1+(1-\mu^O)^2K\right)} & \text{if} \quad v'_O < v < \overline{v}_O \\ 0 & \text{if} \quad \overline{v}_O \leqslant v \end{cases} \tag{2.14}$$

The results in Equations 2.13 and 2.14 define three threshold values for v under the Opaque ERP regime: $\underline{v}_O$, v'_O and $\overline{v}_O$. They are summarized in Figure 2.3, depending on the level of v with respect to these threshold values. Notice that if $\mu^O = 0$ the Opaque scenario would be akin to the Transparent ERP.

Figure 2.3: Optimized variables under Opaque ERP



Under the Opaque ERP regime, $\underline{v}_O = \left(\frac{1}{2} - \sqrt{c}\right)\left(1-\mu^O\right)$ is the "no-launch threshold". However, since at $d^O|_{\underline{v}_O} = 1$ the secret discount is equal to 0 (there is no incentive to concede a discount where there is no entry), the no-launch threshold under Opaque ERP coincides with the Transparent ERP. Similar to the Transparent ERP regime, the "non-negative quantity threshold" identifies the values of v below which M finds it optimal to launch in F at a net price that matches the Foreign regulator's willingness to pay. This threshold is now equal to $v'_O = \frac{1-\mu^O}{2+(1-\mu^O)^2K}$ and thus, for interior solutions of the optimal secret discount, it is lower than the analogous threshold in the Transparent case. Finally, $\overline{v}_O = \frac{\sqrt{K(1-\mu^O)^2+1}-1}{K(1-\mu^O)}$ is the "no-delay threshold" in under Opaque ERP, above which M finds it optimal to launch in both markets at the same time. Again, for interior solutions of the optimal discount, the no-delay threshold is lower than that associated with the Transparent ERP regime.

Proposition 2.3. *The no-launch threshold value under the Opaque ERP, $\underline{v}_O$, coincides with that under the Transparent regime, $\underline{v}_T$. At the same time, v'_O is lower than v'_T and, similarly, $\overline{v}_O$ is lower than $\overline{v}_T$.*

For interior solution of μ^O, it can be seen that $p_F^O > p_F^T$ and $p_F^O > p_F^S$ for any $v \leqslant 1$, meaning that the introduction of secret discount allows the Manufacturer to charge higher

list prices in the Foreign market as compared to the Transparent ERP regime—and, thus, to the Segmented markets regime.

Proposition 2.4. *Under a model of Opaque ERP, the introduction of a strictly positive secret discount in the Foreign market leads to the optimal list price* $p_F^O(\mu^O)$*, such that* $p_H^S > p_F^O(\mu^O) > p_F^T > p_F^S$ *for any* $v \leqslant 1$ *and for interior solutions of* μ^O*.*

Proposition 2.4 provides an insight that is coherent with the intuition: since the concession of secret discount is commonly viewed as the response by manufacturers to the wide adoption of ERP regulations, it is reasonable to expect that, when ERP is triggered, the uniform price p_F^O would fall somewhere between the monopoly price in the Home market, p_H^S, and the Transparent uniform price, p_F^T. This holds for an interior solution of μ^O, which, however, cannot be solved algebraically. Nevertheless, I can infer from visual inspection and from the sign of the second derivative of the maximization problem that it is indeed quasi-concave with respect to μ and has an interior solution such that $\mu^O \in (0,1)$.

As for the optimal discount, from the fourth FOC (Equation 2.12) we can express it as a function of the optimal Foreign price and of the optimal delay (see Appendix A.2.2 for the derivation). The optimal discount always goes in the opposite direction of the optimal delay, if the latter is strictly positive. Also, the optimal discount, as expected, is decreasing with the cost parameter b. If, however, $b=0$ is imposed, the optimal discount would be simply as follows:

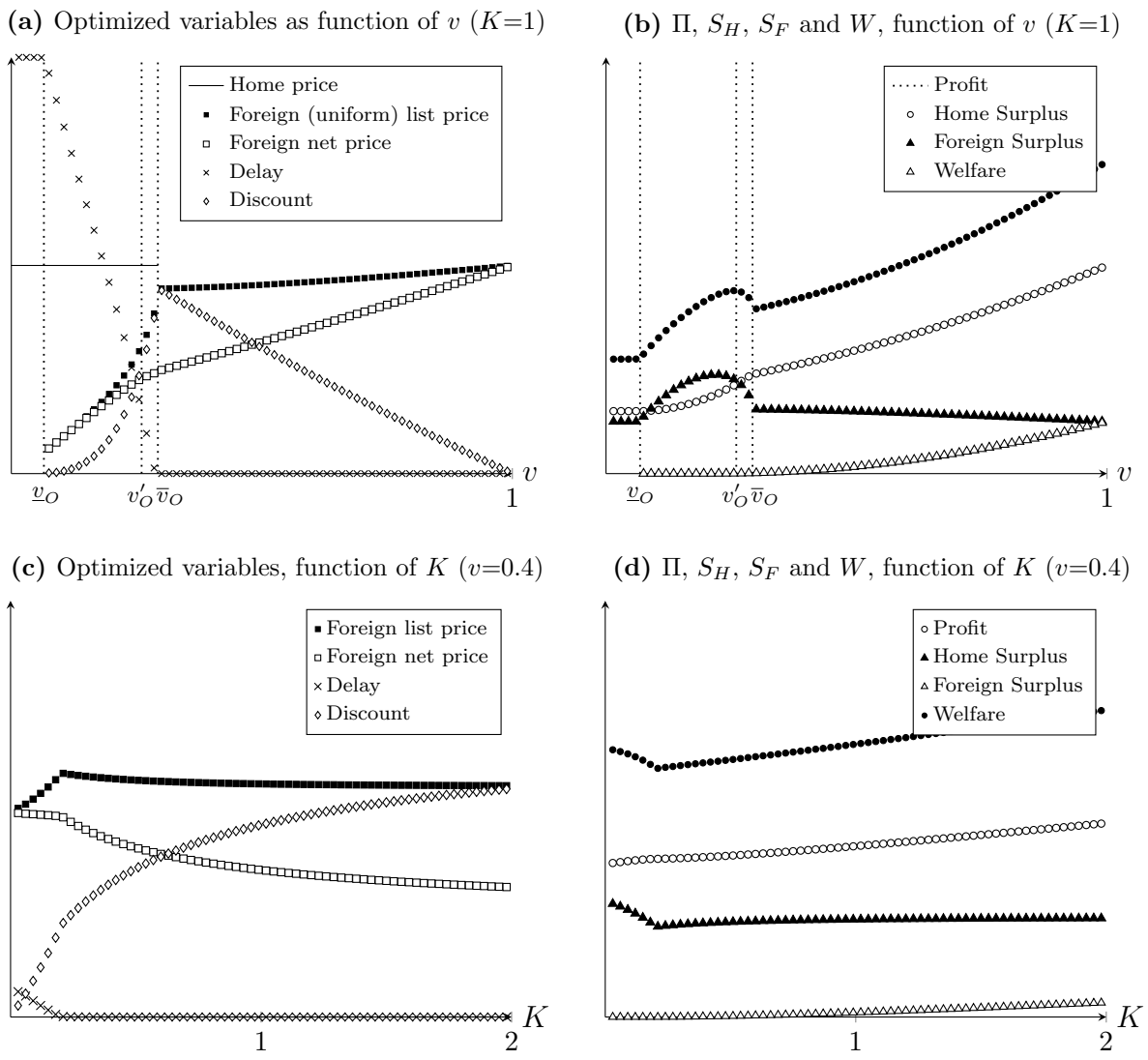
$$\mu^O|_{b=0} = 1 - \frac{v}{2p_F^O} \tag{2.15}$$

Equation 2.15 shows that, when the discount is optimally set without any effort to hide it, the Manufacturer simply restores the monopoly price in the Home market through the uniform list price, while maintaining the monopoly *net* price in the Foreign market. In the following Section, I provide a numerical solution to the maximization problem of Equation 2.8 for p_H, p_F, d and μ.

2.2.3 Numerical Solution

In this Section, I provide the results of the simulation of the profit maximization of Equation 2.8. Figure 2.4 plots the results, assuming that the cost parameters for the delay, c, and for the secret discount, b, are both fixed and equal to 0.2. In particular, Figure 2.4a shows the optimized variables set by M as function of v, and 2.4b shows the optimal values of Profit, Surpluses, and total Welfare as a function of v. Similarly, Figure 2.4c and 2.4d report the same outcomes as a function of K. Moreover, in Figures 2.4a and 2.4b the no-launch, the non-negative quantity, and the no-delay thresholds are reported as dotted vertical lines.

Figure 2.4: Results of the optimization problem under Opaque ERP



It is clear how, between the no-launch threshold $\underline{v}_O$ and the no-delay threshold $\overline{v}_O$, M sets the optimal combination of strictly positive values of delay and secret discount (Panel 2.4a). Specifically, at the no-launch threshold $\underline{v}_O$ the optimal delay is at its maximum ($d^O|_{\underline{v}_O} = 1$) and the secret discount is at its minimum ($\mu^O|_{\underline{v}_O} = 0$), while at the no-delay threshold the optimal delay is at its minimum ($d^O|_{\overline{v}_O} = 0$) and the secret discount is at its maximum ($\mu^O|_{\overline{v}_O}$). After reaching its maximum, for $\overline{v}_O < v$ the secret discount starts decreasing with v. Moreover, at $\overline{v}_O$ the Home surplus starts decreasing in v, following the increase in the Foreign list price (Panel 2.4b). The Home country benefits the most from the Opaque ERP regime when v is between the no-launch threshold $\underline{v}_O$ and the no-delay launch threshold $\overline{v}_O$—as

mentioned, this corresponds to a combination of strictly positive delay and secret discount. The Foreign surplus (Panel 2.4b) is increasing in v, although equal to zero for $v < v'_O$. Finally, the total Welfare is increasing in v for $\overline{v}_O < v$, as the Foreign list price (which should be considered as the uniform price) approaches what would have been the monopoly price in the Home market. The values of Welfare as function of v present the same "hump" as the Home surplus between $\underline{v}_O$ and $\overline{v}_O$.

Panel 2.4c highlights that, holding v constant, the secret discount increases with K. In fact, the incentive to allow secret discounts increases with the size of the Foreign market. The Foreign list price increases with K when M delays the launch in F ($d^O > 0$), whereas it decreases with K when there is no delay and the two entries are contemporaneous ($d^O = 0$). It can be noticed that the decrease of the net price is faster than the decrease of the list price, reflecting the greater market power of the Foreign country due to the larger market size. Finally, Panel 2.4d shows that the profit is always increasing in K. The Home surplus is decreasing with K in correspondence the Foreign list price increase; when the delay reaches its minimum, it is mostly flat. The combined effect of M's profit and of the Home surplus drive the total Welfare.

2.3 Results

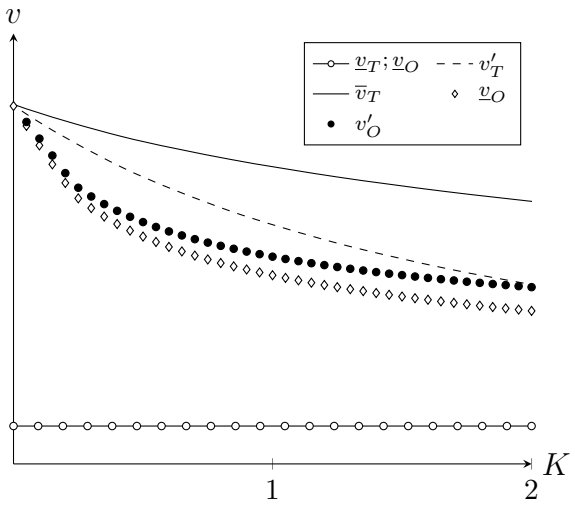
Based on the analysis presented in Section 2.2, in the present Section I address the implications of banning confidential agreements by allowing only the Transparent form of ERP. First, Figure 2.5 displays the no-launch thresholds, the non-negative quantity thresholds, and the no-delay thresholds in the two ERP regimes (Proposition 2.3). The ban of Opaque ERP would raise v' and $\overline{v}$ thresholds. In other words, when prevented from setting the optimal secret discount, M enters in F with zero quantity sold for a greater range of value of v, while it enters both markets with no delays for a narrower range of v's levels. In particular:

$$\underline{v}_T - \underline{v}_O = \left(\frac{1}{2} - \sqrt{c}\right)\mu^O = 0 \tag{2.16}$$

$$v'_T - v'_O = \frac{\mu^O\left[2 - \left(1-\mu^O\right)K\right]}{\left[2 + \left(1-\mu^O\right)^2 K\right](2+K)} \tag{2.17}$$

$$\overline{v}_T - \overline{v}_O = \frac{\left(1-\mu^O\right)\sqrt{K+1} - \sqrt{1+\left(1-\mu^O\right)^2 K} + \mu^O}{\left(1-\mu^O\right)K} \tag{2.18}$$

Figure 2.5: Thresholds under the two ERP regimes

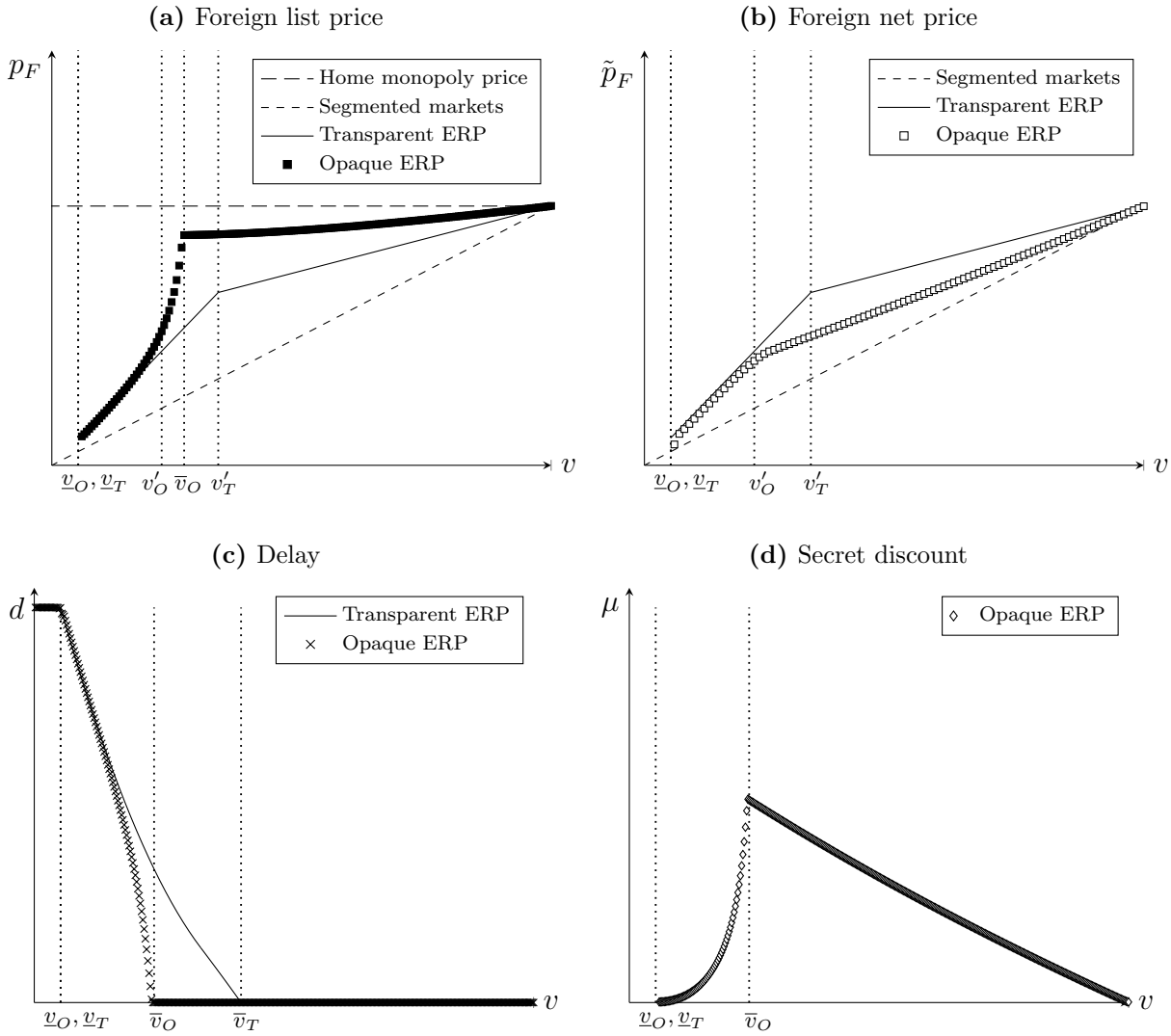


Both $v'_T - v'_O$ and $\overline{v}_T - \overline{v}_O$ are strictly increasing with μ^O and K, meaning that the greater the magnitude of the optimal secret discount, the wider the difference between the thresholds of the two regimes. This is suggestive that banning confidential agreements could potentially decrease the range of values of v such that the reference country experiences zero delays and increase the range of values of v for which the product cannot be afforded by F, but it would have no impact on the no-launch decision by M. In fact, no-launch decisions seem to depend entirely on the cost parameter of the delay, c.

As a reference, Figure 2.6 compares the optimized choice variables under the two ERP regimes and the Segmented markets scenario, for different values of v. Panel 2.6a confirms Proposition 2.4: the introduction of a secret discount under the Opaque ERP regime raises the Foreign list price. The maximum difference between the Transparent Foreign list price and the Opaque Foreign list price corresponds to a level of v equal to $\overline{v}_T$. Foreign list prices under both ERP regimes are higher than the price resulting from the Segmented markets regime. Conversely, the net price paid by the Foreign regulator falls indeed between the Foreign list price under Transparent ERP and the Foreign list price in force under Market Segmentation (Panel 2.6b). Panel 2.6c confirms what is shown in Figure 2.5: the no-launch decision remains the same, while the threshold $\overline{v}_T$ above which M chooses to launch in both markets at the same time is significantly lower under the Opaque regime. The maximum difference in launch delays in the two regimes is at $v{=}\overline{v}_O$. Panel 2.6d displays the optimal level of secret discount μ^O, which is increasing between $\underline{v}_O$ and $\overline{v}_O$, reaching its maximum at $v{=}\overline{v}_O$ and decreasing for $\overline{v}_O < v$.

Figure 2.7 compares Profit, Surpluses, and the total Welfare under the three regimes.

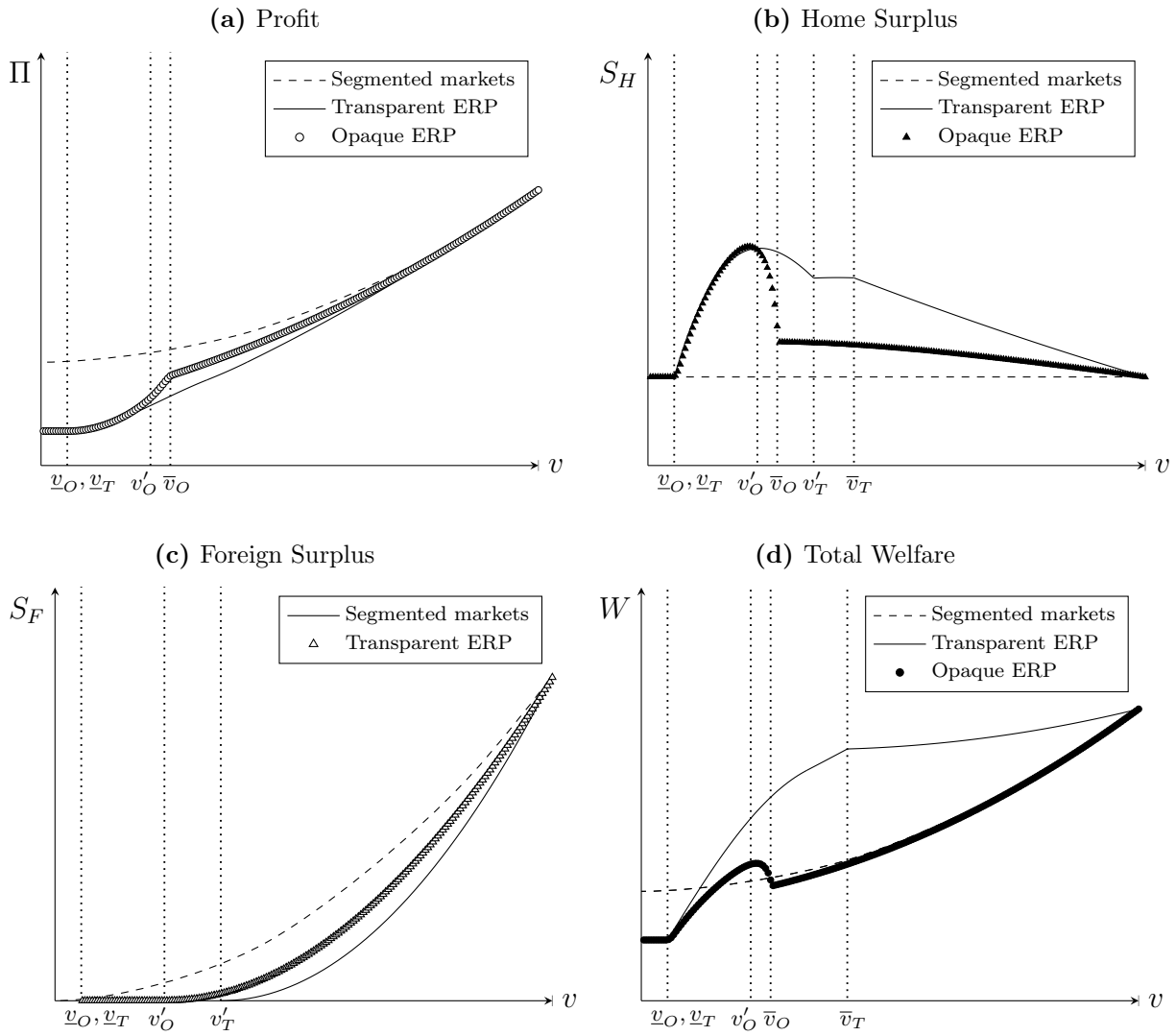
Figure 2.6: Optimized variables under two ERP regimes



In particular, Panel 2.7a compares M's profits. It shows that both types of ERP harm the Manufacturer, who is better off if it can fully price discriminate, in line with the economic theory. A ban on confidential agreements would further harm M, especially when H includes in its basket a country F with the level of v around $\overline{v}_O$—where the difference between W^T and W^O is maximum.

As for the Home country, Panel 2.7b shows that, for extremely low levels of v, there would not be any change with respect to Market Segmentation, as M would simply choose not to launch in F ($v < \underline{v}_O, \underline{v}_T$) and thus the uniform price would not be triggered and the Home market would remain unaffected. For values of v just above the no-launch threshold, both ERP systems are increasingly effective as long as the resulting uniform price is relatively low.

Figure 2.7: Profit, Home and Foreign Surplus, and Total Welfare under two ERP regimes



However, the positive effect on the Home surplus is counteracted by the optimal delay decision and, in case of the Opaque ERP, by the optimal secret discount that raises the Opaque uniform list price. The maximum difference between the two ERP regimes is, again, at $\overline{v}_O$, where H can benefit the most from the Transparent regime by including in its reference set a Foreign country for which M would be just indifferent between setting a delay or not under the Opaque ERP scheme. For a higher level of v, the difference between the three scenarios decreases as v approaches the value of 1.

Panel 2.7c shows that F is worse off after its inclusion in H's ERP set under both ERP regimes. However, since the Transparent uniform price is higher than the Foreign net price, the ban on confidential agreements would penalize F for every value of v.

Finally, Panel 2.7d shows the sum of Profit and Surpluses under the different scenarios. For sufficiently low levels of v, the regime that ensures the highest total welfare is Market Segmentation, as it prevents the no-launch option by M and, even when ERP allows M to enter the Foreign market (for $\underline{v}_O, \underline{v}_T < v$), it can still be preferable if v is low enough. Overall, the Transparent ERP regime is associated with the highest welfare for a sufficiently high level of v: this is almost entirely driven by H's Surplus. In terms of Welfare, the Opaque ERP regime is outperformed by the Transparent ERP for any level of v, but it is still better in terms of total welfare than market segmentation in the range between $\underline{v}_O$ and $\overline{v}_O$—outside of this range, it delivers the lowest total Welfare. This is in favor of the idea that confidential agreements render ERP ineffective, to the point that restoring complete Market Segmentation would be preferable from a total Welfare point of view.

2.4 Discussion and Conclusions

External reference pricing (ERP) is often used as a policy measure of cost containment for pharmaceutical spending. Each domestic ERP regulation is based on publicly available prices (or "list prices") of a pre-determined list of "reference countries". List prices, however, do not always represent what payers pay for medicines because of the presence of confidential agreements between the payer (identified by the health authority) and the manufacturer, often in the form (but not limited to) of secret discounts. The emergence of such discounts can be seen as a response by manufacturers to the widespread adoption of ERP schemes. In this way, they can circumvent the cause that prevents them from effectively price-discriminate across different markets. The empirical evidence available suggests that this tool is often used in combination with strategic entry delays and price increases in reference countries. However, no previous work has rationalized the use of confidential discounts in the presence of ERP, accounting for launch timing decisions. Such effort can contribute to the debate over the economic consequences, at the European level, of a ban on confidential agreements in favor of more transparency.

I developed a model with two countries (Home and Foreign) and a Manufacturer serving both markets. Home adopts ERP by referring to the Foreign price, when available, and the Manufacturer sets the price in the two markets, the launch sequence of new drugs, and the secret discount on the Foreign list price. The price ceiling, once it becomes binding for the ERP adopter, also becomes the uniform price of the economy. Throughout the model, I distinguish and compare three scenarios: *i)* Segmented markets, where there is no ERP in place; *ii)* Transparent ERP, where the Home country adopts ERP and refers to the Foreign

country but the Manufacturer cannot set confidential discount; and *iii)* Opaque ERP, where instead, the Manufacturer is allowed to concede a secret discount to the Foreign list price.

In general, the adoption of any type of ERP by a national regulator is beneficial for the adopter. At the same time, ERP is detrimental to the reference country and to the manufacturer. The wide reliance on confidential agreements—what I model as a secret discount conceded by manufacturers to the reference countries—can attenuate the negative effect of ERP both on the manufacturer and on the reference country, and, in fact, they are both better off without transparency. Nevertheless, the model suggests that a ban on the Opaque type of ERP in favor of Transparent ERP would increase total Welfare. This implies that such bans would disproportionately favor the adopter at the expense of the manufacturer and the reference country. This holds true for sufficiently high levels of willingness to pay of the reference country.

From a policy perspective, the following considerations can be drawn from the comparison of the levels of total Welfare under the three regimes, shown in Figure 2.7d. First, the ERP adopter should refrain from including countries with extremely low levels of willingness to pay for pharmaceuticals in its reference set. In fact, this can lead to a no-launch decision for the manufacturer in the foreign market, and on top of this, it renders the ERP policy itself ineffective for the adopter and harmful for the total Welfare—regardless of the ERP regime. Second, a total ban on confidential agreements, which would, in turn, impose the Transparent ERP regime, can potentially increase the delay of the market entry in reference countries with low-to-middle levels of willingness to pay, but it does not affect no-launch decisions by firms (Figure 2.6c). In other words, the model suggests that more transparency should not lead to fewer markets reached by innovative products, but it might lead to longer delays in low-medium income countries. Third, a ban on confidential agreements overall increases total Welfare as long as the ERP is triggered—thus, for values of willingness to pay of the reference country above the no-launch threshold of the firm. This effect is entirely driven by the ERP adopter, whose benefit more than compensates the negative effect that the ban would have on the Manufacturer and the reference country. Fourth, the ban on confidential agreements is associated with a lower uniform list price, but the reference country ends up paying a higher price compared to what was paid had the discount being conceded (Figure 2.6a). This is in line with Riccaboni et al. (2022) and Gamba et al. (2020) for the European market, and with Feng et al. (2023), who find evidence that price transparency in the Medicaid program in the US could potentially lead to overall higher price levels in the long run. From the second and the third point, it is possible to draw the conclusion that if a supranational policymaker is to design a compensation scheme to make the ban on Opaque ERP mechanisms politically

viable, it should consider the direct involvement of the ERP adopter. For instance, a form of mitigation could be either a direct transfer by the adopter for the inclusion of the reference country in the ERP basket. This might explain, in part, the emergence of groups of countries coordinating to negotiate the price of pharmaceuticals with manufacturers.

Therefore, the answer to whether supranational regulators should advocate for more transparent settings depends on the weight that is given to each agent involved and the compensation scheme that is proposed to mitigate the adverse effect on the manufacturer and on the reference country. The present analysis, however, does not focus on the adoption *per se* of ERP schemes as compared to other mechanisms—although price discrimination might seem desirable when the ERP adopter and the candidate reference country differ substantially in terms of willingness to pay. This might indeed be the focus of future research.

Chapter 3

Strategic Response to External Reference Pricing

S. Gamba, P. Pertile, G. Righetti

Abstract *In years of growing pharmaceutical spending, regulators have exerted substantial effort to reduce the impact of this tendency. Several countries have introduced External Reference Pricing (ERP) as part of their strategy. This is a mechanism through which the domestic price is linked to a benchmark price, based on publicly available pricing data from a number of foreign countries where a price has already been set. This creates potentially complex mechanisms of strategic interaction at the international level. The focus of this paper is to document the consequences of one country being included in the ERP reference set of another country. We use a simple theoretical model to show that introducing ERP in one country may increase the marginal impact of foreign prices on the global profit of the manufacturer of the new product. As a result, we expect higher prices to be negotiated in foreign countries. Our empirical analysis uses a dataset of 65 anticancer drugs in 16 countries and exploits the introduction of ERP in Germany in 2011 as part of the AMNOG bill. The results confirm our theoretical predictions: the introduction of ERP in Germany led to a 6.7% price increase in reference countries.*

Keywords Pharmaceutical regulation, diff-in-diff, ERP, spillovers

JEL codes I18, L51, C78.

3.1 Introduction

In recent years, global spending on medicines has been constantly increasing worldwide (GCO, 2020). Numerous efforts have been put in place to contain such rapid expansion, especially in the European pharmaceutical market (Vogler et al., 2011). Several European regulators have adopted External Reference Pricing (ERP) as part of their strategy, while the US is still considering its implementation.[1] The practice of ERP consists of using the price of a new medicine in one or several countries, which together comprise the ERP reference set, in order to define a reference price to be used as a benchmark (WHO, 2013). This benchmark is used for setting or negotiating the price of new products, and the criteria for the selection of the ERP reference set may include geographical proximity, country income, availability of medicines, country of origin, and market size (Espin et al., 2014; WHO, 2020b). Although ERP is applied quite heterogeneously across countries, it has the common aim of ensuring that they do not overpay for new medicines with respect to their neighbors.[2] The wide reliance on ERP scheme potentially creates complex mechanism of cross-country interactions at the international level.

In the adopting countries, ERP schemes have proven to be a successful cost-containment measure through significant price reductions (Kanavos et al., 2020).[3] Moreover, there is evidence that the widespread reliance on ERP schemes leads to a general downward price convergence (Csanádi et al., 2018; Kaló et al., 2015; Leopold et al., 2012). The results of these studies are also in line with the predictions made by Toumi et al. (2014), Vogler et al. (2020) and Stargardt and Schreyögg (2006), who simulated the impact of the extensive use of ERP across the EU over time. In general, ERP policies limit the ability of manufacturers to price discriminate across countries, reducing pharmaceutical companies' profits (Danzon, 1997). One of the countermeasures adopted by the pharmaceutical industry has been to strategically delay launches of new medicines in countries with more stringent regulations (Cockburn et al., 2016; Danzon et al., 2005; Heuer et al., 2007; Kyle, 2007), or in low-income countries, in order

[1] As of today, there is a lack of consensus on what would be the impact (Dubois et al., 2022; Frank et al., 2022; Mulcahy et al., 2021). The H.R. 3 (Elijah Cummings Lower Drug Costs Now Act) set a ceiling on the outcomes of a price negotiation process between the government and pharmaceutical companies. Although the ERP provision in the final version of the legislation was dropped in 2021, it shaped the political debate over ERP (Frank et al., 2022). For instance, the Trump administration proposal in 2018 put forward an ERP mechanism for all drugs covered by Medicare's Part B program but was blocked in 2020 by a federal judge (Frank et al., 2022).

[2] See Table A.3.1 for an overview of ERP use in Europe. See also, among others, Rémuzat et al. (2015), Espin et al. (2014) and Kanavos et al. (2020) for a review.

[3] An exception is represented by Denmark moving *from* ERP to internal price referencing in 2005. Kaiser et al. (2014) reported a substantial reduction in retail prices. Nevertheless, Denmark came back to an ERP-informed system a few years later, in 2009, but limited to in-hospital medicines.

to avoid the propagation of low prices and attenuate the harmful impact of ERP (Lanjouw, 2005; Maini and Pammolli, 2023).

The consensus is that the inclusion of a country in the reference set of the ERP adopter weakens the bargaining position of the reference country with respect to the manufacturers, leading to higher prices. This is coherent with similar policies that limit price discrimination, such as parallel trade (Malueg and Schwartz, 1994), Most-Favored-Customer Clause (MFCC) (Scott-Morton, 1997) or internal reference pricing (Brekke et al., 2009). In the case of ERP, this general agreement comes mainly from theoretical studies (Ackermann, 2010; Birg, 2016; Garcia Mariñoso et al., 2011; Geng and Saggi, 2017). Moreover, the structural model of Dubois et al. (2022), estimated the impact of the adoption of an ERP policy in the US, arguing that its introduction would result in much smaller price decreases in the US than price increases in reference countries. Nevertheless, empirical evidence, to the best of our knowledge, is still missing.

This paper aims to fill part of this gap by analyzing the domestic and international consequences of ERP adoption by one country. Our empirical analysis exploits a reform that was introduced in Germany in 2011, the AMNOG bill.[4] The reform explicitly included an ERP criterion among the rules prescribed for the price negotiation process between the producer of new innovative pharmaceutical products and the regulator. Specifically, the bill provided a list of countries whose prices should inform the benchmark price for the negotiation. We introduce a simple model that allows us to investigate both some mechanisms associated with the adoption of ERP previously discussed in the literature and some specific aspects of the AMNOG reform that can be empirically tested. The adoption of ERP by one country increases the marginal impact of prices set in countries used as reference on the manufacturer's global profit. This leads to an increase in the price negotiated in the reference country. We refer to this impact as *strategic effect of ERP*. We show that the magnitude of this effect increases with the market size of the country adopting ERP relative to the referenced country and with the stringency of the ERP criterion introduced.

The empirical analysis employs the IMS Health pricing database, which includes a panel of quarterly prices for anticancer drugs in 25 OECD countries from 2007 to 2017.[5] Consistent with the theoretical predictions, we provide evidence of a price increase in countries included in the German ERP reference set after the reform, relative to the other countries. To the best of our knowledge, this is the first contribution that provides empirical evidence of the impact of the adoption of ERP by one country on prices set in countries included in its reference set.

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

[5] Following the merge between IMS Health and Quantiles, IMS has been renamed IQVIA.

The present work contributes to three strands of literature. The first is the theoretical literature that investigates the cross-country implications of ERP adoption taking into account optimal responses of profit-maximizing manufacturers. In particular, Garcia Mariñoso et al. (2011) and Geng and Saggi (2017) show that the introduction of an ERP scheme in one country can increase prices negotiated in countries included in its reference set, the magnitude of such increase depending on the commitment by the Home country to engage in ERP. Our work empirically tests their predictions. Secondly, our work is related to the broader literature on regulatory provisions that, by limiting price discrimination, generate spillovers across markets. Among others, there are contributions on internal reference pricing (Brekke et al., 2009),[6] generics competition (Brekke et al., 2016; Frank and Salkever, 1997), parallel trade (Brekke et al., 2015; Dubois and Sæthre, 2020; Duso et al., 2014; Ganslandt and Maskus, 2004; Grossman and Lai, 2008), and Most-Favored-Customer Clause (MFCC) (Feng et al., 2023; Scott-Morton, 1997).[7] Finally, the present paper contributes to the assessment of the (unintended) consequences of the 2011 AMNOG reform in Germany. To the best of the author's knowledge, the only estimate of the causal impact of the reform, along with the evidence presented in Chapter 1, has been provided by Büssgen and Stargardt (2022). Their staggered difference-in-differences model shows that the AMNOG reform led to an additional market entry delay of 4.31 months in Germany relative to other countries. Rather than on the consequences in Germany, we focus on the unintended spillover effect on reference countries. This effect, if present, can, in turn, reduce the effectiveness of the AMNOG reform itself as a measure to curb domestic drug prices.

The present work proceeds as follows: Section 3.2 describes the AMNOG reform; Section 3.3 proposes a simple theoretical framework of strategic effect of ERP; Section 3.4 sets out the identification strategy and the data, and Section 3.5 presents the results. Finally, Section 3.6 summarizes the findings and concludes the work.

3.2 Institutional Background

Marketing authorization of medicines has been harmonized in the EU and, since 1995, it falls under the competence of the European Medicines Agency (EMA). Once new drugs are granted market approval, pharmaceutical companies can conclude contracts with public payers. In fact, pricing and reimbursement are national competences of the EU Member

[6] Internal reference pricing involves the setting of a maximum reimbursement price to be paid for a group (or "cluster") of drugs.

[7] To a large extent, ERP can be regarded as an international MFCC (Feng et al., 2023).

States, provided they are compliant with the EU Transparency Directive.[8] Several EU countries rely on statutory pricing, *i.e.* they set the price on a unilateral basis—only a few (e.g. France, Italy) have price negotiations as the sole pricing procedure. However, as noted by Vogler and Martikainen (2014): "*in many European countries statutory pricing is accompanied by negotiations, particularly when it comes to reimbursement and (confidential) discounts may be granted.*" Nevertheless, German pharmaceutical prices prior to 2011 were neither set by governmental agencies, nor negotiated between manufacturers and the regulator, but determined by manufacturers (Stargardt, 2011). Nevertheless, this freedom, "*rather exceptional in an international comparison*" (Greiner et al., 2022), was still subject to a strict regulatory framework and cannot be compared to other unregulated markets, such as the US.

The Federal Parliament (Bundestag) of Germany introduced, in 2011, a new HTA procedure, the *Act to Reorganize the Pharmaceuticals Market* (AMNOG). The bill, which came into force in January 1st 2011, kept the principle of free pricing at launch while imposing a formal assessment of the added therapeutic benefits of new drugs, in order to allow price negotiation to be based on the therapeutic value.[9] In particular, for the negotiation process to start, the manufacturer must submit a report with the clinical evidence of the new drug, which is assessed by the relevant authority. In case the added therapeutic benefit is confirmed, the bill prescribes a round of negotiations to set the reimbursement price between the Federal Association of Sickness Funds (SHI) and the manufacturer, in consultation with the Association of Private Health Insurance Companies. This process lasts for a total of 12 months, under which the free price set by the manufacturer remains in force before the new agreed-upon price takes over.

The negotiation takes into account the added value of the drug, the annual cost of therapy of other comparable pharmaceuticals, and, most importantly for our analysis, the price level of a bundle of countries, defined as "reference set". The countries included in the reference set are Belgium, Denmark, Finland, France, UK, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Spain, and the Czech Republic. The price level is 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).[10]

[8] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

[9] For orphan drugs with annual revenue of less than € 50 Million per year, market authorization is considered proof of additional benefit by German regulations. Above this threshold, orphan drugs are assessed as conventional drugs (Ruof et al., 2014).

[10] The bill (in German) is available at the following link; https://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/rahmenvertraege/pharmazeutische_unternehmer/Rahmenvereinbarung_130b_Abs9__SGB_V_2016.pdf.

Because of the reliance on the EU price level, German pharmaceutical regulation can be thought of as having a "mild" or "supportive" form of ERP (Rémuzat et al., 2015). The agreed price applies from the second year, i.e. from the 13$^{\text{th}}$ month after market introduction, but not retroactively to the first year. Moreover, the agreement is valid without a time limit (Wenzl et al., 2018). In case no agreement is reached after twelve months, an Arbitration Board examines the case. Until 2015 only 15% of all negotiations ended up in the arbitration stage (Ludwig and Dintsios, 2016). Finally, drugs with no additional therapeutic benefits are included in a fixed reimbursement group or, if this is unfeasible, a price is negotiated that should not be higher than the price of the appropriate comparator (Greiner et al., 2022).

3.3 Theoretical Framework

We define as Home country (H) the country introducing the ERP policy, as Foreign country (F) the country that is included in Home's reference basket, and as Manufacturer (M) the producer and seller of a patent-protected pharmaceutical product i, which can serve both markets. The adoption of the product occurs as a result of a successful negotiation between the Manufacturer and each national regulator. In line with the existing literature (Dubois et al., 2022; Garcia Mariñoso et al., 2011; Jelovac, 2015; Pecorino, 2002), we assume that the pricing process, especially in the EU context, is based on Nash bargaining.[11] It is also assumed that the product is negotiated first in F and then in H. No renegotiation takes place. The size of the market of H is normalized to 1, with K denoting the market size of F. We assume that individuals are homogeneous within a country, but they differ across countries in the money equivalent of their valuation of the product. This is normalized to 1 in H and equal to v in F, with $v < 1$.[12] We assume that the demand for product i is inelastic and all patients eligible for the treatment are identical. The assumption of perfectly inelastic demand is realistic for innovative, high-cost drugs, whose price we assume is fully reimbursed by the payer.[13] The Manufacturer aims to maximize total profit for each product i, denoted as $\Pi_i = \pi_i^H(p_{iH}) + \pi_i^F(p_{iF})$, where π_i^H and π_i^F are respectively the profits made in H and M, whereas p_{iH} and p_{iF} are the respective prices. Regulators in H and F aim to

[11] Although some authors provided an alternative framework with a profit-maximizing firm, without negotiation. This is the case of Geng and Saggi (2017) from which the analysis in Chapter 2 is drawn.

[12] In the absence of the hypothesis that $v < 1$, it is possible that the introduction of ERP by H leads to an increase in prices, which would make it a suboptimal decision. However, this assumption is irrelevant to the impact of interest, i.e., the impact of adopting ERP in H on F's price.

[13] The demand for pharmaceuticals has been found to be reasonably price inelastic (see, for the antiulcer drug market in the US, Berndt et al., 1995). However, given our theoretical set-up, relaxing this assumption with a linear demand for pharmaceuticals would not affect the quality of our results. Full reimbursement for new innovative drugs appears to be a reasonable assumption in the EU context.

maximize consumer surplus, which is respectively $S_{iH} = 1 - p_{iH}$ and $S_{iF} = (v - p_{iF})K$. We assume that, in case of negotiation failure, the product is not adopted. In that case, we normalize to zero the value of S_{iH} and of S_{iF} (the so-called "disagreement payoffs").[14] We set up a two-stage game: first, the Manufacturer bargains with the Foreign country over the price p_F (M *vs* F negotiation); secondly, it bargains with the Home country over the price p_H (M *vs* H negotiation).[15] In both stages, the price resulting from the bargaining between country $c \in \{H, F\}$ and the Manufacturer is obtained through the solution of the standard Nash bargaining problem:

$$\arg\max_{p_c} \left[\Delta S_c(p_c)\right]^{\gamma_c} \left[\Delta \Pi^c(p_c, p_{-c})\right]^{1-\gamma_c} \tag{3.1}$$

where $\Delta S_c(p_c)$ is the incremental consumer surplus and $\Delta \Pi^c(p_c, p_{-c})$ is the incremental profit in case the negotiation is successful, as compared to the payoffs in case the negotiation fails.[16] The bargaining solution involves two Nash bargaining solutions between the firm and each regulator, given that the other negotiation has reached an agreement. In other words, we rely on the "Nash-in-Nash" solution concept (Horn and Wolinsky, 1988). The dependency of the profit made in c, $\Delta \Pi^c$, on the other country's price (p_{-c}) allows us to consider the spillover effects related to the adoption of ERP. As usual, γ_c (with $0 < \gamma_c < 1$) is the bargaining power of the regulator. In what follows we solve the problem backward, first in the benchmark scenario where no ERP is adopted in H, then in the scenario with ERP.

3.3.1 No ERP in the Home country

In this case, the negotiations in the two countries take place independently of each other. Starting from the negotiation taking place in H, the price resulting from the Nash bargaining negotiation is obtained by solving:

$$\tilde{p}_H = \arg\max_{p_H} (1 - p_H)^{\gamma_H} \, p_H^{1-\gamma_H}, \tag{3.2}$$

which leads to the definition of the price in H in the scenario without ERP, $\tilde{p}_H = 1 - \gamma_H$. This price depends on the patient benefit (1 for H) and it is decreasing in the regulator's bargaining power. Since in the absence of ERP the price determination in each country takes

[14] This is similar to Jelovac (2015) and to the "tough threat scenario" in Garcia Mariñoso et al. (2011). Garcia Mariñoso and colleagues also explore the "weak threat" scenario, where in case of negotiation failure the product is just de-listed and not reimbursed—ultimately leading to a situation akin to the monopolist's price maximization. Our choice eases the computational burden without affecting the results.

[15] In what follows, subscripts i denoting the product are dropped to simplify the notation.

[16] The superscript for Π refers to the country in which the price negotiation is undertaken.

place independently of the other, the same steps can be repeated to study the determination of the price in F:

$$\tilde{p}_F = \arg\max_{p_F} \left[(v - p_F)K\right]^{\gamma_F} \left[p_F K\right]^{1-\gamma_F}, \tag{3.3}$$

which leads to $\tilde{p}_F = v(1-\gamma_F)$.

3.3.2 Home country adopts ERP

Under the ERP scenario, the Home country relies on ERP and refers to the Foreign country. 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, $\tilde{p}_H$, with weight $1-\alpha$, and the price of the Foreign country, with weight α, with α between 0 and 1.

$$p_H = (1-\alpha)\tilde{p}_H + \alpha p_F. \tag{3.4}$$

This definition allows for different levels of "ERP intensity", as measured by the parameter α. This is important from the policy perspective, given that ERP rules adopted in different countries can be very heterogeneous in terms of stringency, ranging from very mild forms, such as a broad indication of which countries will be taken as reference in price regulation, to precise formal rules as average prices computed over a certain set of countries. If $\alpha=0$, ERP has no impact on price decisions and the price equals the price in the absence of the ERP: $p_H|_{\alpha=0}=\tilde{p}_H$. In case $\alpha=1$, the ERP criterion would be the only one considered by the Home country regulator in setting i's price—country H simply "borrows" the price set by the Foreign country regulator once product i is adopted, so that $p_H|_{\alpha=1}=p_F$. In this case, the ERP rule replaces the negotiation process that led to price determination in the previous subsection. However, given the way in which we model ERP, $\tilde{p}_H$ still plays a role. Country H's price with ERP can be rewritten as $p_H=(1-\alpha)(1-\gamma_H)+\alpha p_F$.

Equation 3.4 introduces a dependency between the prices set in H and F, which has consequences for the bargaining taking place in F, through the manufacturer's total profit, which is now equal to $\Pi=(1-\alpha)(1-\gamma_H)+\alpha p_F + Kp_F$. We start by assuming that the weight of the foreign price in the determination of p_H is independent of any characteristic of F. We will relax this assumption later to account for a specific characteristic of the ERP criterion adopted by Germany in 2011. In case of failure of the negotiation in F, the Manufacturer would still be able to sell the product in the Home market. However, in the absence of a price negotiated in F, there would be no price cap. Therefore, the incremental payoff would be equal to $\Delta\Pi^F=(1-\alpha)\tilde{p}_H+\alpha p_F + Kp_F - \tilde{p}_H$, where $\tilde{p}_H$ is the disagreement profit of the firm.

Hence, F's price for the scenario with ERP in H is determined by solving:

$$p_F^* = \arg\max_{p_F} [(v - p_F)K]^{\gamma_F} \left[(1-\alpha)(1-\gamma_H) + \alpha p_F + p_F K - \tilde{p}_H \right]^{1-\gamma_F} \tag{3.5}$$

with $\tilde{p}_H = 1 - \gamma_H$. The first order conditions lead to the optimal price equal to:

$$p_F^* = v(1-\gamma_F) + \frac{\alpha\gamma_F(1-\gamma_H)}{\alpha + K}. \tag{3.6}$$

To investigate the impact of the strategic effect of ERP, we focus on the difference between the prices set in F with and without ERP:

$$\theta \equiv p_F^* - \tilde{p}_F = \frac{\alpha\gamma_F(1-\gamma_H)}{\alpha + K} \geq 0. \tag{3.7}$$

Proposition 3.1 (Strategic effect of ERP)**.** *The introduction of the ERP criterion in the Home country always raises prices in the Foreign country, for any value of α, K, γ_H and γ_F.*

The intuition underlying Proposition 3.1 is straightforward: the adoption of ERP by H has a spillover effect on prices negotiated in F because an increase in these prices leads to higher prices in H, other things being equal. This effect is similar to those previously discussed in Garcia Mariñoso et al. (2011) and Geng and Saggi (2017) and predicted by Dubois et al. (2022). Table 3.1 below summarizes the optimal prices and quantities under the two scenarios: independent price negotiation and after the adoption of ERP.

Table 3.1: Summary of theoretical predictions

Indep. Neg.	*ERP*	Δ
$\tilde{p}_F$	$\tilde{p}_F + \theta$	$+$
$\tilde{p}_H$	$\tilde{p}_H - \alpha\left[\tilde{p}_H - (\tilde{p}_F + \theta)\right]$	$-$
$\tilde{S}_H$	$\tilde{S}_H + \alpha\left[\tilde{p}_H - (\tilde{p}_F + \theta)\right]$	$+$
$\tilde{S}_F$	$\tilde{S}_F - \theta K$	$-$
$\tilde{\Pi}$	$\tilde{\Pi} + \alpha\left[\tilde{p}_F - \tilde{p}_H(1-\gamma_F)\right]$	$+/-$

Of particular interest in view of our empirical analysis is the relationship between the relative market size (K) and the magnitude of the strategic effect. To investigate this aspect, we introduce a specific generalization of the model by allowing α to depend on K, meaning that the size of the weight of F's price in the determination of H's price via ERP depends on the size of F's market. The reason why we allow for this is that this provision is part of the ERP mechanism introduced in Germany in 2011. The following equation describes the

comparative statics of the strategic effect with respect to K for this more general case:

$$\frac{d\theta}{dK} = \frac{\left[\gamma_F(1-\gamma_H)\frac{d\alpha}{dK}\right](\alpha+K) - \left(\frac{d\alpha}{dK}+1\right)\left[\gamma_F(1-\gamma_H)\alpha\right]}{(\alpha+K)^2} \tag{3.8}$$

the sign of which may be positive or negative. However, a sufficient condition for $\frac{d\theta}{dK}$ to be negative is that $\frac{d\alpha}{dK} \leq 0$. Therefore, if, as is commonly the case, the weight of the foreign country price in the ERP rule is independent of its market size ($\frac{d\alpha}{dK} = 0$), the size of the spillover effect is smaller the larger the size of F's market. This is due to the fact that a larger market size in F, *ceteris paribus*, makes the difference between a successful and unsuccessful negotiation in F larger, making the manufacturer willing to accept a lower price.

In the case of the ERP rule introduced in Germany in 2011, the weight is increasing in the size of the foreign market ($\frac{d\alpha}{dK} > 0$). This introduces an additional effect operating in the opposite direction to the one commented above. Therefore, whether the impact on foreign prices increases or decreases with the size of the foreign market is an empirical question, which will be addressed in Section 3.5. The following corollary summarizes the comparative statics with respect to K.

Corollary 4. *If the weight of the foreign price is independent of (decreasing in) the size of the referenced market, the price increase in the referenced country is larger the smaller its market size. If the weight of the foreign price is increasing in the size of the referenced market the price increase in the referenced country may increase or decrease with its market size.*

Equation 3.7 also shows that the size of the strategic effect increases with α and with the bargaining power γ_F. Unlike for K, the data we use for our empirical analysis do not allow us to test these additional predictions.[17]

3.4 Empirical Analysis

In the previous Section, we outlined the strategic responses related to the inclusion of one country into another country's ERP reference set. The AMNOG reform implemented in Germany in 2011 prescribed explicit ERP considerations as a supportive criterion in the price negotiation process between the German regulator and the manufacturer of new innovative products. Referring to our theoretical model, this implies an increase in the value of the parameter α from zero (no ERP) to a value between 0 and 1. Hence, our empirical analysis

[17] Even assuming that α could be measured, we would have no variability in the data, because in the observation period Germany is the only country to introduce ERP. In the case of the bargaining power, γ_F, measurement is particularly challenging.

exploits this reform and the fact that only some countries are included in the German reference set to test the theoretical predictions related to the impact of the introduction of ERP on the prices of countries included in the German ERP reference set. In particular, we expect to observe higher prices in these countries after the AMNOG reform. We will also test the prediction that the size of the market of the country included in the reference set affects the size of the impact on prices (Corollary 4).

We employ the Two-Way Fixed Effects (TWFE) model in Equation 3.9 for our main specification. We decided to adopt the observed entry prices as the dependent variable rather than using multiple observations for each product in each country over time. We believe that the strategic effect, as we define it, operates mostly on the price negotiation process before launch rather than on price revisions once the product is already in the market. Besides, there is very limited price variation over time. In particular, the entry prices considered are the first reimbursed price of the product. The strategic effect can affect the entry prices (through the national negotiation processes) of products launched within the first 12 months after the same product is launched in Germany: this time span corresponds to the negotiation window prescribed by the AMNOG reform in Germany, so that those products launched during that time window in a country that is included in the German ERP set can, in principle, be considered in the AMNOG negotiation process, and thus be subject to the strategic effect.

$$lnPrice_{ict} = \alpha + \beta STRAT_{ict} + \delta_1 lnPREV_{ict} + \delta_2 PRODAGE_{it} + \delta_3 lnGDP_{ct} + \\ + \delta_4 EXRATE_{ct} + \zeta_i + \eta_t + \theta_c + \epsilon_{ict} \quad (3.9)$$

The dependent variable $lnPrice_{ict}$ is the natural logarithm of the entry price in Euro of product i for country c at time t. $STRAT_{ict}$ is a dummy variable equal to 1 if the observation simultaneously satisfies two conditions: country c belongs to the reference set of Germany, and product i was launched in country c after 2011. Therefore, β can be interpreted as the difference in differences estimator and represents our coefficient of interest. $lnPREV_{ict}$ is the natural logarithm of total prevalence at time t in country c of the disease(s) that can be treated by product i and is a proxy for market size. The correlation between market size and pharmaceutical prices has been explored both theoretically and empirically (Egan and Philipson, 2013; Frech et al., 2023; Helble and Aizawa, 2017; Kyle and Qian, 2014; Puig-Junoy and López-Valcárcel, 2014), although the evidence on the role of this parameter is still not conclusive. Pertile et al. (2023) show that there may be more than one mechanism, possibly operating in opposite directions, linking market size to pharmaceutical prices. $lnGDP_{ct}$ is the natural logarithm of GDP per capita in International Dollars. Similar to other empirical

studies (Cabrales and Jiménez-Martín, 2013; Kyle and Qian, 2014; Leopold et al., 2012; Pertile et al., 2023), this variable is included to account for payers' ability to pay. $PRODAGE_{ict}$ represents the time, in years, since the first launch of product i in any country included in our sample. This variable is intended to be a proxy for the degree of obsolescence of a product, as the evidence suggests that prices tend to fall over time (Cabrales and Jiménez-Martín, 2013; Danzon and Chao, 2000; Kanavos and Vandoros, 2011). $EXRATE_{ct}$ is the exchange rate (Euros per one unit of local currency). These are the same exchange rates used to obtain our dependent variable starting from prices in local currency. Therefore, if changes in exchange rates were immediately and fully accounted for in price setting, meaning that only prices in Euro matter, the coefficient associated with $EXRATE_{ct}$ would be zero. By including this variable in our specification we allow for the possibility that changes in the value of the local currency do affect negotiated prices expressed in Euro. This may occur, for example, if changes in the exchange rate are expected to be transitory and price re-negotiations are not foreseen to take place shortly. In this case, we would expect the relevant coefficient to be greater than zero and smaller than one, the upper extreme corresponding to a situation where only the price in local currency matters.

Finally, we include product (ζ_i), country (θ_c) and year (η_t) fixed effects. The product fixed effect is intended to capture drug i's quality and therapeutic advance, both of which are unobserved. Including product fixed effects is also essential because we use prices per mg, and the standard course of treatment strongly varies across drugs. Year fixed effect captures country- and product-invariant shocks to prices. Country fixed effect captures differences among countries in the average price level.

Our identification relies on the parallel trend assumption (PTA). Specifically, we assume that the difference between prices of products launched in countries included in the German ERP bundle and prices of those launched in countries that are excluded, remained the same had the AMNOG reform not been introduced. A threat to the PTA can arise if national regulators have changed the pricing process of pharmaceuticals over time. However, only minor changes occurred: only Belgium and Denmark substantially changed the way ERP is implemented during the time period of interest (Maini and Pammolli, 2023). This is tested in Section 3.5.2. Moreover, there has been no significant change in AMNOG legislation since 2011 (Stern et al., 2019). We also assume that Germany has not changed the way it sets prices in the first 12 months since each product's market authorization. If that was the case, the prices in countries that adopt an ERP criterion and include Germany in the reference set could be biased, and the impact of such bias on the strategic effect of countries included in the German ERP set would be ambiguous. The work of Lauenroth et al. (2020) and the

analysis in Chapter 1 (Section 1.5.1 on the opportunistic behavior by manufacturers) seem to exclude that possibility. Another possible threat is posed by the change of the entry order or, in general, of the launch schedule of new products across countries due to the reform. In fact, manufacturers might have systematically anticipated or postponed the launch of products across countries depending on their ability to influence German prices through the AMNOG's ERP criterion. If that is the case, our analysis would include only a selection of treated entry prices after the reform—most likely those with relatively higher prices—and thus we should expect our results to be biased upward. This is discussed and tested in Section 3.5.2.

3.4.1 Data

The empirical analysis is conducted using the Pricing Insights IMS database.[18] IMS price data are particularly suitable for price comparisons among a large number of countries, and for this reason they have been already used in other studies.[19] Data on quarterly prices and information on the date of launch were retrieved for 85 non-generic anticancer drugs, sold in 25 OECD countries in the period 2007–2017 (see Table A.3.1 and A.3.2 in the Appendix).[20] Even though it would be interesting to extend the analysis to several therapeutic areas, cancer stands out as the most interesting domain for several reasons. In recent years, anticancer treatments have seen probably more innovation than any others, which led to substantial impacts on the survival and quality of life of patients. Partly as a result of this, expenditure in this area grew substantially (Hofmarcher et al., 2020; Mariotto et al., 2011). In Germany, from 2011 when AMNOG entered into force to the end of 2020, 291 drugs underwent the assessment and the price negotiation process, 32% of which treated cancers (Greiner et al., 2022).

Given our focus on regulated prices, we exclude the United States from the analysis. Greece is also omitted because of the impact that the financial crisis on pharmaceutical prices (Vandoros and Stargardt, 2013). Additionally, Portugal is omitted because the Pricing Insights IMS Health database provides only a very partial coverage for the period of interest. All prices are converted into Euro using the quarterly exchange rate reported in the Pricing

[18] The company, IMS Health, was subsequently renamed IQVIA.

[19] See, among others, Danzon and Chao (2000), Von der Schulenburg et al. (2011), Kyle and Qian (2014), Cabrales and Jiménez-Martín (2013) and, more recently, Dubois and Lasio (2018) and Dubois et al. (2022).

[20] During this time span EMA authorized 108 antineoplastic drugs, but 25 of these had to be excluded: 6 do not treat cancer, 3 treat some types of cancer for which prevalence data are not available from our source, 2 are hybrid drugs which lack the degree of innovation that is central in our analysis (a hybrid drug contains the same active substance as an authorized drug, but differs on some other characteristics such as strength, indication or pharmaceutical form). In addition, 10 were not on patent in any country in our sample during the period of analysis, and 2 are included in the original EMA list, but not in our price data set because of their very recent market launch. Finally, 2 drugs are lost because they were introduced only in the US.

Insights IMS database. Also, prices have been recalculated to refer to a milligram (mg) of active substance. This choice is intended to make products, that might be sold with different pack sizes or different strengths, more comparable within and across countries. When different prices are available for the same product at the same time within one country, the lowest price per mg is considered, assuming that this is the relevant price for a rational payer. Data for prevalence, measured by the number of individuals suffering from a disease in a given year, are extracted from the Global Burden of Diseases (GBD) 2015 database (Vos et al., 2016). We refer to EMA therapeutic indication(s) of the drug to match each drug to one or more of the 28 "Level 3" neoplasm causes identified by the GBD 2015 database, with dubious cases resolved by referring to the opinions of two medical doctors, one for hematology and one for oncology. When more than one indication is expressed by EMA, we refer to the sum of all diseases' prevalence. Prevalence data are only available at five-year intervals, thus prevalence is considered constant within the intervening four years. Finally, data for GDP per capita in International Dollars are gathered from the World Bank Indicators. Variables included in the analysis are presented in Table 3.2.

Table 3.2: Variables employed in the analysis

Variable	*Type*	*Definition*	*Source*
lnPrice	cont.	Natural log of quarterly price per mg	Pricing Insights IMS database
Product age	cont.	Time in years since the product launch in the first country of launch.	Pricing Insights IMS database
lnPrev	cont.	Natural log of the prevalence of diseases treated by product i in country c.	GBD 2015 database
lnGDP	cont.	Natural log of GDP per capita.	World Bank Indicator
Exchange Rate	cont.	The rate at which the local currency is converted in Euro	Pricing Insights IMS database

Of the 85 products, we consider the subset of 65 products with at least one market entry potentially subject to the strategic spillover—that is, observed before the negotiated price is in force in Germany—with a total of 570 entry prices across 16 countries.[21] The final sample

[21] From the 65 product we retrieved a total of 640 entry prices across countries, from which we omitted 3 outliers (Spectrila in UK, Arzerra in Poland and Opdivo in Japan) as they show a distance from the average entry price of the same product (own price excluded) above 100%. Moreover, 14 observations were excluded because the date at which the price is first available does not correspond to the launch date as reported in the dataset. In this case, the observation cannot be safely regarded as an entry price. Finally, from the remaining 623 observed entry prices we have excluded those that belong to countries for which we have data only after the reform (Czech Republic, Japan, Korea, Luxembourg and Slovakia).

is shown in Table 3.3.

Table 3.3: Sample considered for the empirical analysis

Included	*First obs*	*Pre*	*Post*	*Excluded*	*First obs*	*Pre*	*Post*
Austria	Q1 2007	14	50	Hungary	Q3 2008	2	3
Belgium	Q1 2007	12	22	Norway	Q1 2007	13	42
Denmark	Q3 2007	14	47	Poland	Q4 2010	1	4
Finland	Q1 2007	11	25	Switzerland	Q2 2007	8	30
France	Q1 2007	12	32	Turkey	Q3 2010	1	1
Ireland	Q3 2007	12	25				
Italy	Q1 2007	9	21				
Netherlands	Q3 2008	3	22				
Spain	Q1 2007	13	15				
Sweden	Q1 2007	10	33				
UK	Q1 2007	16	48				
		126	340			25	80

Included: countries included in the German ERP set and thus subject to the strategic spillover; *Excluded*: countries excluded from the German ERP set; *Pre*: entry prices before AMNOG reform; *Post*: entry prices after AMNOG reform.

Table 3.3 shows all countries included in the analysis, the different coverage across countries and the number of entry prices observed in each country, before and after the introduction of the AMNOG bill.

3.5 Results

Table 3.4 provides the results of the TWFE model, with standard errors clustered at the product level and country, year, and product fixed effects. Column 1 shows the main regression, which includes the set of explanatory variables and the fixed effects. The coefficient of interest suggests that the adoption of ERP by Germany in 2011 led to an average price increase of 6.7% (p–value=0.018) for countries belonging to the German ERP set. As expected, product obsolescence has a significant negative impact: an additional year from the first launch across all markets is associated with a 6.6% reduction in entry price. Neither GDP per capita nor prevalence are statistically significant: one possible reason is that the effects are already captured by the country fixed effect.[22] The coefficient associated with the exchange rate is equal to 0.383, and it is statistically significant ($p = 0.005$), suggesting that, to some extent, the value of prices in local currency matter, irrespective of the corresponding value expressed in an international (Euro) currency.

[22]Excluding country fixed effect and leaving all else the same, we obtain a positive and significant coefficient for GDP per capita, although the effect of prevalence remains statistically equal to zero.

Table 3.4: Strategic spillover effect of AMNOG reform

	Main	*No 2011*	*No BE, DK*
Dep. Var.: ln Price	(1)	(2)	(3)
Strategic	0.067**	0.068**	0.078***
	(0.027)	(0.028)	(0.028)
Ln prev	-0.017	-0.013	-0.018
	(0.020)	(0.024)	(0.026)
ln GDP pc	-0.167	-0.173	-0.142
	(0.149)	(0.153)	(0.155)
Time since first launch (in years)	-0.066*	-0.115***	-0.063
	(0.036)	(0.031)	(0.043)
Exchange rate	0.383***	0.338**	0.377***
	(0.131)	(0.135)	(0.130)
Constant	3.021*	3.063*	2.755
	(1.610)	(1.670)	(1.699)
Product FE	Yes	Yes	Yes
Country FE	Yes	Yes	Yes
Year FE	Yes	Yes	Yes
Observations	570	536	475
R^2 adjusted	0.998	0.998	0.998

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

Column 2 shows the results of the same specification with the exclusion of the observations that occurred during the year 2011. In fact, during the first year after the reform manufacturers were provided some leeway to comply with the new legislation (Büssgen and Stargardt, 2022). The coefficient of interest associated with the strategic spillover is still positive and significant, with a similar magnitude to the main model. Finally, the model in Column 3 excludes the two countries that underwent minor policy changes, such as Belgium and Denmark. Again, the results are coherent with those of the preferred specification in Column 1.

3.5.1 Impact of Market Size of Reference Countries

In the present Subsection, we address the impact of the market size of reference countries relative to the size of the ERP adopter (denoted as K in Section 3.3). We consider the (expected) prevalence of the disease that is targeted by each product as the proxy for the market share considered by the agents when negotiating the price of the product. Given the fact that the prevalence of the product launched in Germany (the ERP adopter) is fixed, the prevalence of each product launched elsewhere can also be considered as the market share relative to that of Germany. With this reasoning, we construct the dummy variable $ABOVE$ equal to 1 if the prevalence associated with each product is above the median prevalence for

the same product across countries, and equal to zero otherwise. The framework in Section 3.3 does not provide any clear cut prediction, as the overall effect is driven by whether the weight given by the Foreign price depends on the size of Foreign market covered by the product. Table 3.5 provides the results.

Table 3.5: Impact of Market Size of Reference Countries

Dep. Var.: ln Price	(1)	(2) above	(3) below
Strategic		0.100***	0.036
		(0.034)	(0.030)
Strategic=1 × above=1	0.053**		
	(0.023)		
Ln prev	-0.024		-0.013
	(0.022)		(0.027)
ln GDP pc	-0.118	-0.541*	0.081
	(0.150)	(0.298)	(0.170)
Time since first launch (in years)	-0.072*	-0.085*	-0.086**
	(0.038)	(0.047)	(0.041)
Exchange rate	0.375***	0.362***	0.298
	(0.127)	(0.135)	(0.333)
Constant	2.581	6.883**	0.465
	(1.611)	(3.169)	(1.784)
Observations	570	354	354
R^2 adj.	0.998	0.998	0.998

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

In Column 1 we interacted the variable *STRAT* with the dummy *ABOVE*. The resulting coefficient is positive and significant, suggesting that the strategic effect is higher for products with prevalence above the median. This is confirmed also by splitting the sample in two, depending on whether each observation is associated with a product above or below the median prevalence. This is in contrast with the prediction that the strategic effect should increase the larger (smaller) the market share of Germany (of the reference country). This might be explained by the fact that the larger the market share of the reference country, the more relevance it gets in the AMNOG's ERP criterion during price negotiation.

3.5.2 Robustness checks

Placebo tests We perform a leave-one-out analysis by excluding one country at a time from our main specification. This is to rule out that our main results are driven just by one country. The results are shown in Table A.1.5 and A.1.6, and they appear quite consistent across models, both in terms of the magnitude of the coefficients of interest and in terms of

their significance.

Table 3.6: Leave-one-out analysis/1

DV: lnPrice	AUT	BEL	DNK	FIN	FRA	HUN	IRL	ITA
STRAT	0.0756**	0.0796***	0.0748***	0.0745***	0.0646**	0.0737**	0.0679**	0.0690**
	(0.0289)	(0.0285)	(0.0265)	(0.0274)	(0.0257)	(0.0288)	(0.0282)	(0.0290)
Expl. Var.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Obs.	504	533	506	531	523	563	530	537

Table 3.7: Leave-one-out analysis/2

DV: lnPrice	NLD	NOR	POL	ESP	SWE	CHE	TUR	UK
STRAT	0.0706**	0.0680	0.0778***	0.0663**	0.0812***	0.0689**	0.0668**	0.0594*
	(0.0278)	(0.0490)	(0.0277)	(0.0278)	(0.0286)	(0.0286)	(0.0277)	(0.0299)
Expl. Var.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Obs.	542	512	562	539	524	531	565	503

The only exception is represented by the model that excludes Norway. However, the coefficient of the variable of interest remains positive and has a similar magnitude to the other coefficients; therefore, we cannot rule out that it is simply a less precise estimate due to the limited number of observations. This is suggestive that the results are not driven by any single country alone.

Table 3.8 shows the estimates of the effect of a number of placebo reforms that occurred in different periods—also referred to as "in-time placebo" test. We constructed four different variables of interest that are alternatives to the binary variable $STRAT$ in the main analysis: $STRAT1$, $STRAT2$, $STRAT3$, and $STRAT4$. In detail, $STRAT1$ is equal to 1 if country c belongs to the German ERP set and product i in country c is launched in the period 2009-2011, and equal to 0 if the same product i in country c is launched in the period 2007-2009. $STRAT2$ is equal to 1 if country c belongs to the German ERP set and product i in country c is launched in the period 2011-2013, and equal to 0 if it is launched in the period 2009-2011. $STRAT3$ and $STRAT4$ are constructed in an analogous way. The only variable of interest to show a significant effect is $STRAT2$, which is associated with a placebo reform occurring in 2011—as the AMNOG reform. This hints at the fact that the effect is not driven by change, but that is due to the AMNOG reform in 2011.

Finally, we perform a placebo randomization, whose results are displayed in Figure 3.1. In particular, we look at the estimates of our variable of interest obtained by randomizing both the country undergoing the AMNOG reform (with its own ERP set) and the time of the intervention from the main model. It can be observed in the top panel of Figure 3.1 that

Table 3.8: In-time placebo test

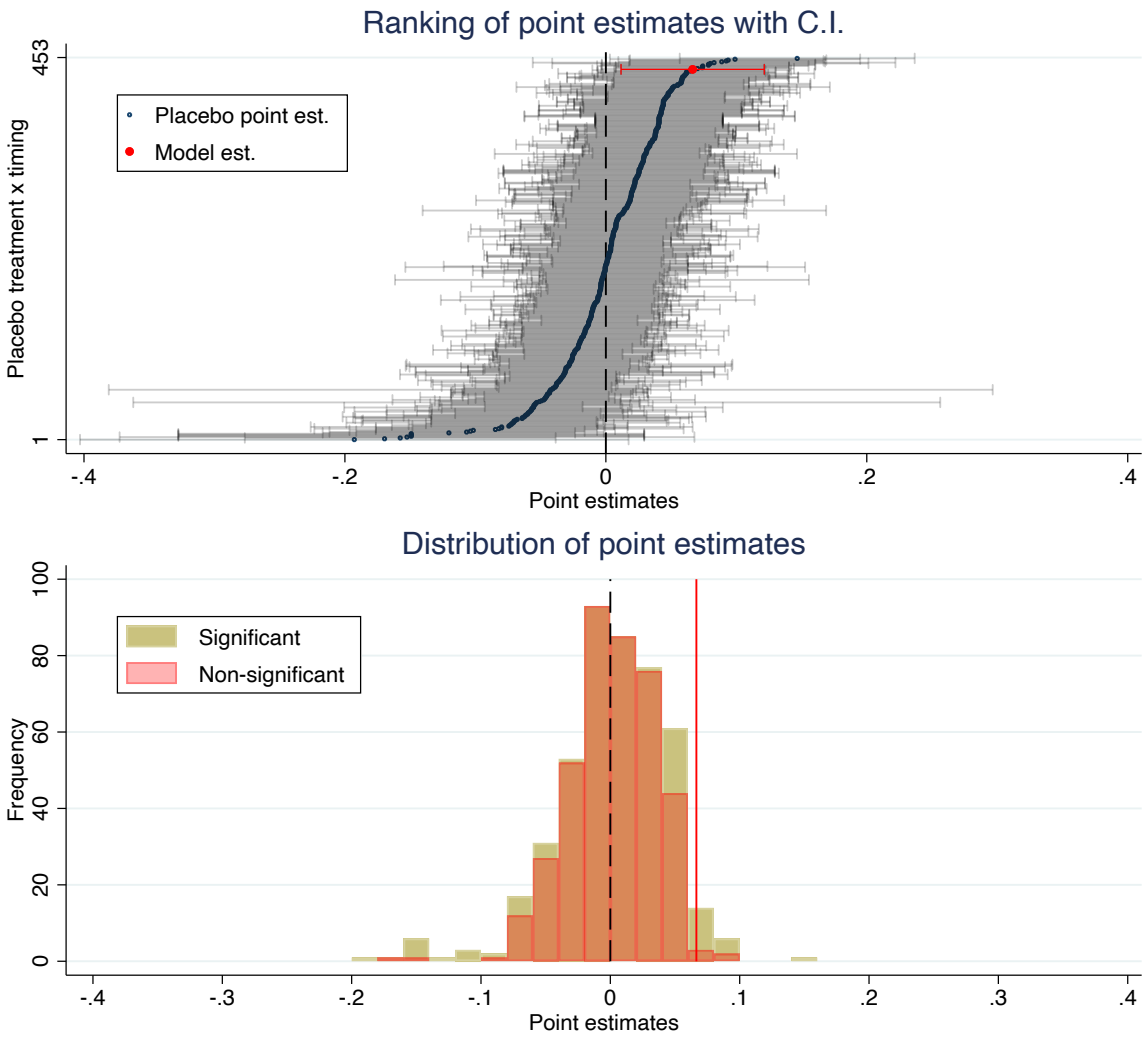
DV: ln Price	(1)	(2)	(3)	(4)
STRAT1	-0.003			
	(0.111)			
STRAT2		0.113***		
		(0.032)		
STRAT3			0.020	
			(0.023)	
STRAT4				0.044
				(0.032)
Expl. Vars.	Yes	Yes	Yes	Yes
Product FE	Yes	Yes	Yes	Yes
Country FE	Yes	Yes	Yes	Yes
Year FE	Yes	Yes	Yes	Yes
Observations	102	162	242	329
R^2 adjusted	1.000	0.999	0.997	0.998

our original result is at the extreme of the distribution of the point estimates of all placebo models. In other words, if one were to assign the intervention at random in the data, both in terms of timing and in terms of which country adopts it, the probability of obtaining an estimate with a magnitude as high as the one obtained by our main model is 14/452=0.03097 where 14 are the number of models that obtained an estimate greater than our preferred one (whose point estimate and the confidence interval are marked in red in the Figure). The ratio obtained, 0.03097, is lower than the significance threshold usually employed. This approach is similar to Abadie et al. (2010), and it is suggestive that the price increase was driven by manufacturers actually targeting German prices after 2011.

Instead, the bottom panel of Figure 3.1 shows a frequency histogram of the magnitude of point estimates of all placebo models, given by the combination of all possible timing and adopter of the policy. It can be observed that the peak of the distribution of all point estimates coincides with zero. The red vertical line indicates the magnitude of the point estimate of our preferred model. In orange, the sub-sample of point estimates that are not significant at the 95% confidence level (the share of not significant estimates over the total estimates increases towards zero).

Products' launch schedule Manufacturers might have systematically anticipated or postponed the launch of products across countries depending on their ability to influence German prices through the AMNOG ERP criterion. Specifically, after 2011 manufacturers could have systematically anticipated (postponed) the launch of high-priced (low-priced)

Figure 3.1: Placebo Randomization



Top Panel: on the y-axis are stacked all possible 453 combinations of time of the placebo intervention and the placebo regulator, ranked from the combination with the highest point estimate for $STRAT$ to the lowest. On the x-axis is the point estimate, with the 95% confidence interval. The result of our preferred estimation is highlighted in red. *Bottom Panel:* The red vertical line indicates the point estimates of our preferred model. Frequency histogram of the magnitude of point estimates of all placebo models. In orange, the point estimates that are not significant at the 95% confidence level.

products to be included in (excluded from) the ERP consideration within the AMNOG process. If that is the case, our analysis would include only a selection of treated entry prices after the reform—most likely those with relatively higher prices—and thus we should expect our results to be biased upward. To test this, we adopted two approaches. The first is to look, across products, at the lag in quarters between each country's launch date and the

German launch date. Specifically, we compare, for each country, the cumulative distribution of such lags of products launched before 2011 with that of products launched after 2011. In Table 3.9 we report the exact $p-$values of the Kolmogorov-Smirnov (K-S) tests for equality of distributions. All countries but Belgium, Ireland and Spain failed to reject the null hypothesis

Table 3.9: Test for equality of distributions of lags from German launch, pre- and post-2011

Country	*Exact P-value*	*Country*	*Exact P-value*
Austria	0.993	Netherlands	1.000
Belgium	0.000***	Norway	1.000
Denmark	0.919	Poland	0.725
Finland	0.820	Spain	0.008***
France	0.563	Sweden	0.397
Hungary	0.654	Switzerland	0.644
Ireland	0.047**	Turkey	0.115
Italy	0.444	UK	0.491

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Exact $p-$values of the two-sample Kolmogorov-Smirnov test for equality of distribution of launch lags from German launch, pre- and post-2011, by country.

of equal distributions. In these three countries the cumulative distribution function after the reform is shifted to the right (see Figure A.3.1 in the Appendix), suggesting that the average launch date with respect to the one in Germany increased after 2011. This is suggestive that manufacturers did not anticipate the relatively most expensive products to influence German prices: if anything, they could have postponed the least expensive *not* to influence German prices. Nevertheless, the exclusion of these three countries does not alter our results (Table A.3.3 in the Appendix).

The second approach is intended to capture the fact that, after 2011, manufacturers might have anticipated the entry date of the most expensive products to ensure they fall within the reach of the AMNOG ERP criterion and, at the same time and with the same proportion, they might have postponed the least expensive ones. This mechanism would not be detected by the approach above, as the cumulative distribution of launch lags would be significantly different between pre- and post-reform. To test it, we rely on the model in Equation 3.10.

$$POSTG_{ict} = \beta_0 + \beta_1 \left(HIGH_c \times Post_{ict}\right) + \beta_2 HIGH_c + \beta_3 Post_{ict} + \\ + \mathbf{X}_{ct} + \zeta_i + \eta_t + \theta_c + \epsilon_{ict} \quad (3.10)$$

The dependent variable $POSTG_{ic}$ is a binary variable equal to 1 if product i in country c is launched within one year since the launch in Germany, and equal to zero otherwise. The variable $Post$ is equal to 1 if product i in country c is launched after 2011. $HIGH_c$ is another

binary variable equal to 1 if pre-reform prices in country c are high relative to German prices. To construct the dummy $HIGH_c$ we divided the sample based on whether the average entry price of anticancer drugs prior to 2011 was above or below the average pre-reform entry prices in Germany. Finally, the set of covariates $\mathbf{X}$ and the fixed effects are the same as in the main specification (Equation 3.9). Our interest lies in the coefficient of the interaction term $HIGH \times Post$: it tells us the probability change, after 2011, of a product from high-priced countries relative to the same product in low-priced countries entering within a year after the German launch. A positive and significant coefficient would imply that the probability has increased after the AMNOG reform, suggesting that manufacturers have successfully anticipated the market entry of the most expensive drugs because of the introduction of the ERP criterion. Table 3.10 provides the results of four specifications, corresponding to four different configurations of the model presented in Equation 3.10.

Table 3.10: Launching order depending on the country's price level.

Dep. Var: POSTG	(1)	(2)	*Treated*	*Controls*
Post=1 × HIGH=1	-0.033	-0.065	-0.015	-0.244
	(0.063)	(0.062)	(0.065)	(0.444)
Post=1	-2.406***	-0.029	-0.254	0.747
	(0.247)	(0.497)	(0.632)	(1.322)
HIGH=1	0.061	-0.018	0.131	3.041
	(0.062)	(0.147)	(0.154)	(2.303)
Constant	2.229***	-1.282	1.059	32.068
	(0.100)	(3.022)	(3.430)	(22.756)
Expl. Vars.	No	Yes	Yes	Yes
FE	Yes	Yes	Yes	Yes
Observations	747	747	586	161
R^2 adjusted	0.621	0.646	0.648	0.697

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

The model in Column 1 excludes covariates, while the model in Column 2 includes them. Columns 3 and 4 replicate the model in Column 2 but are limited to products launched in countries included in the German basket and excluded from it, respectively. None of the coefficients of the interaction terms between $Post$ and $HIGH$ is significant; their $p-$values are 0.604, 0.299, 0.819 and 0.584, respectively. It appears that, in general, having a relatively high price level before the reform does not lead to earlier launches after the reform. Both approaches presented above support the idea that the price increase resulted from manufacturers' price bargaining efforts rather than a change in their launch schedule across countries included in Germany's ERP set.

3.6 Discussion and Conclusion

It is accepted that the widespread reliance on ERP schemes can, on one side, limit the increasing expenditure for health care services, and, on the other, lead to potentially complex interactions among national pharmaceutical regulations. These interactions might attenuate the beneficial effects of such pricing policy and even be harmful to some regulators. The present paper explores the impact of the adoption of ERP in one country on the price setting in countries included in its ERP reference set (the "reference countries"). Our simple theoretical model predicts that the spillover created by the introduction of ERP leads to an increase in prices in the reference countries, The mechanism that we propose is that the marginal impact of drug prices in referenced countries on the global profit of the firm increases, so the price resulting from the negotiation will be higher.

Our empirical analysis relies on the rich Pricing Insights IMS database and exploits a reform that was implemented in Germany in 2011, the new Act to Reorganize the Pharmaceuticals Market (AMNOG). The AMNOG legislation explicitly introduced a list of EU countries to be taken as a benchmark among the new criteria employed in the pricing mechanism of new medicines. This gave manufacturers the incentive to bargain higher prices for products that were launched in countries on that list. Our results confirm that the entry prices of products launched in countries included in the German ERP set, as compared to products launched in countries that were not, are 6.7 percentage points higher after 2011, according to our preferred specification. This seems to suggest that manufacturers successfully raised prices in response to the AMNOG reform. To be more precise, this strategic behavior is to be traced back to the *expectation* that the ERP criterion is used, since the manufacturer, when setting the price for product i in country c, does not know with certainty whether the same product i will be launched in Germany and whether its price will be subject to negotiation. Moreover, we are able to rule out the impact of a change in the launch schedule of new products by manufacturers after the reform. To our knowledge, this is the first empirical measure of the spillover effect from being referenced by another national regulator through the ERP mechanism.

An inevitable limitation of our empirical analysis is that it uses list prices even though, as outlined in more detail in Chapter 2, confidential discounts are agreed upon between the payer and the manufacturer (Morgan et al., 2017; Vogler and Paterson, 2017). Typically, the firm might try to set high list prices and concede a substantial confidential discount to circumvent the propagation of low prices through ERP (Espin et al., 2014). Therefore, we cannot exclude the increase in list prices that we document is, at least partly, compensated by such discounts.

This would reduce the size of the spillover effect. However, even in the extreme case where this effect was completely offset by confidential discounts, which would eliminate the impact on the country included in the reference set, there would still consequences for the country adopting ERP. If the introduction of ERP aims to reduce domestic prices, this goal might not be achieved, due to the strategic reaction that we document, which leads to an increase in the prices that are taken as reference. This might be a particularly serious risk for countries whose markets are comparatively large.

More generally, we provide evidence that the strategic reactions to the introduction of ERP policies that had been mainly studied theoretically until now may have significant practical relevance. As a result, the adoption of ERP may lead to actual results not in line with the expectations of regulators adopting them. A natural question for future research is whether greater coordination of pricing policies at the international level should be considered.

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Appendix A

A.1 The Impact of the AMNOG Reform

A.1.1 Data Set

Table A.1.1: Adoption of ERP criterion and composition of the reference set

Country	*ERP*	*GER in ERP criterion*	*in AMNOG criterion*
Austria	✓	✓	✓
Belgium	✓	✓	✓
Czech Rep.	✓		✓
Denmark	✓	✓	✓
Finland	✓	✓	✓
France	✓	✓	✓
Germany	✓		
Greece	✓	✓	
Hungary	✓	✓	
Ireland	✓	✓	✓
Italy	✓	✓	✓
Japan	✓	✓	
Korea	✓	✓	
Luxembourg	✓	✓	
the Netherlands	✓	✓	✓
Norway	✓	✓	
Poland	✓	✓	
Slovak Rep.	✓	✓	✓
Spain	✓	✓	✓
Sweden			✓
Switzerland	✓	✓	
Turkey	✓		
UK			✓
US			

ERP: countries that rely on ERP criterion in their domestic regulation. *Germany in ERP criterion*: countries that include Germany in their ERP reference set. *in AMNOG ERP criterion* : countries that are referenced by the ERP criterion embedded in the AMNOG bill.

Table A.1.2: Descriptive statistics of each products

Product	*Price (€)*	*S.D.*	*Launch*	*Product*	*Price (€)*	*S.D.*	*Launch*
Abraxane	2.85	0.41	2005q1	Lonsurf	7.33	6.05	2014q2
Adcetris	67.46	10.44	2011q3	Lynparza	0.25	0.07	2014q4
Afinitor	12.37	4.37	2009q1	Mekinist	111.37	28.16	2013q2
Arzerra	2.47	1.00	2009q4	Nexavar	0.16	0.00	2005q4
Atriance	1.29	0.12	2006q1	Ninlaro	660.41	32.68	2015q4
Avastin	3.05	0.11	2004q1	Odomzo	1.53	0.04	2015q3
Blincyto	74034	8648	2014q4	Onivyde	16.50	0.00	2015q4
Bosulif	0.31	0.09	2012q3	Opdivo	17.84	9.62	2014q3
Cabometyx	4.63	1.71	2016q2	Perjeta	6.63	1.09	2012q2
Caprelsa	0.61	0.26	2011q2	Pixuvri	21.08	5.12	2012q2
Cometriq	1.67	0.77	2013q1	Portrazza	2.44	1.16	2015q4
Cotellic	4.49	0.40	2015q3	Spectrila	32.47	22.43	2016q3
Cyramza	6.12	1.22	2014q2	Sprycel	0.94	0.11	2006q3
Dacogen	22.65	5.25	2006q2	Stivarga	1.25	0.62	2012q3
Darzalex	4.85	0.60	2015q4	Sutent	3.39	0.30	2006q1
Empliciti	4.31	0.69	2015q4	Tafinlar	0.75	0.18	2013q2
Erbitux	2.04	0.43	2004q1	Tagrisso	3.02	0.88	2015q4
Erivedge	1.47	0.39	2012q1	Targretin	0.27	0.01	2000q1
Evoltra	47.33	3.27	2005q1	Tasigna	0.16	0.04	2007q3
Farydak	38.37	9.82	2015q1	Teysuno	0.09	0.01	2011q1
Gazyvaro	3.79	0.49	2013q4	Torisel	28.66	2.97	2007q2
Giotrif	1.77	0.82	2013q3	Trisenox	36.75	7.19	2000q4
Halaven	451.19	154.08	2010q4	Tyverb	0.07	0.01	2007q1
Ibrance	2.17	0.99	2015q1	Unituxin	448.93	97.82	2015q2
Iclusig	5.25	1.77	2012q4	Vargatef	0.21	0.04	2014q4
Imbruvica	0.50	0.09	2013q4	Vectibix	4.17	0.59	2006q4
Imlygic	26.29	7.42	2015q4	Venclyxto	0.62	0.10	2016q2
Inlyta	14.21	5.34	2012q1	Vidaza	3.62	0.41	2004q2
Iressa	0.30	0.03	2002q3	Votrient	0.13	0.04	2009q4
Jakavi	3.71	1.17	2011q4	Xalkori	0.37	0.13	2011q3
Javlor	4.26	0.91	2009q3	Xaluprine	0.01	0.00	2012q1
Jevtana	72.84	18.18	2010q3	Yervoy	83.94	11.47	2011q1
Kadcyla	18.10	2.64	2013q1	Yondelis	1816.10	347.20	2007q4
Keytruda	34.87	3.84	2014q3	Zaltrap	4.57	2.83	2012q3
Kisplyx	6.39	0.85	2016q3	Zelboraf	0.14	0.03	2011q3
Kyprolis	21.96	3.22	2012q3	Zydelig	0.49	0.14	2014q2
Lenvima	6.23	0.71	2015q1	Zykadia	0.30	0.11	2014q2

Price: Average price of product across periods and across all countries of the sample. Launch: date of launch of the product; Launch.: date in which the first market entry is reported.

A.1.2 Additional Robustness Tests

Table A.1.3: Strategic spillover effect: exclusion of products launched in 2011

Dep. Var.: Ln price		
Treated × Post × Reg	-0.163***	(0.051)
Treated × Post	-0.014	(0.033)
Treated × Reg	-0.013	(0.015)
Post × Reg	-0.006	(0.018)
Ln prev	-0.022	(0.023)
Ln GDP pc	0.205***	(0.067)
Prod Age	-0.012***	(0.003)
Constant	-0.972	(0.781)
Product, Year, Country FE	Yes	
Observations	13644	
R^2	0.994	
R^2 adj.	0.994	

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

Table A.1.4: In-time placebo test

	(1)	(2)	(3)	(4)	(5)
Treated × Post1 × Reg	0.011				
	(0.032)				
Treated × Post2 × Reg		0.013			
		(0.049)			
Treated × Post3 × Reg			-0.184***		
			(0.057)		
Treated × Post4 × Reg				-0.144**	
				(0.070)	
Treated × Post5 × Reg					-0.004
					(0.063)
Expl. Variables	Yes	Yes	Yes	Yes	Yes
Constant	-3.381***	-2.061**	-0.645	3.982***	2.629
	(0.779)	(0.976)	(0.941)	(1.361)	(1.795)
Product, Year, Country FE	Yes	Yes	Yes	Yes	Yes
Observations	7207	5590	7173	6043	6100
R^2	0.997	0.997	0.996	0.993	0.993
R^2 adj.	0.997	0.997	0.996	0.993	0.993

Standard errors in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. I constructed five different variables that are alternatives to the binary variable *Post* in the main analysis: *Post*1, *Post*2, *Post*3, *Post*4, and *Post*5. *Post*1 is equal to 1 if i in country c is launched in the period 2009-2011, and equal to 0 if the same product i in country c is launched in the period 2007-2009. *Post*2 is equal to 1 if product i in country c is launched in the period 2011-2013, and equal to 0 if it is launched in the period 2009-2011. *Post*3, *Post*4 and *Post*5 are constructed in an analogous way.

Table A.1.5: Leave-one-out analysis/1

	AUT	BEL	CZE	DNK	FIN	FRA	GRC
Treated×Post	-0.164***	-0.160***	-0.173***	-0.161***	-0.165***	-0.157***	-0.172***
×Reg	(0.0444)	(0.0441)	(0.0429)	(0.0445)	(0.0439)	(0.0442)	(0.0437)
Observations	14047	14218	14940	14070	14406	14102	14561
R^2	0.994	0.994	0.995	0.994	0.994	0.995	0.994
R^2 adj.	0.994	0.994	0.995	0.994	0.994	0.995	0.994

Table A.1.6: Leave-one-out analysis/2

	HUN	IRL	ITA	JPN	KOR	LUX	NLD
Treated×Post	-0.162***	-0.158***	-0.166***	-0.158***	-0.169***	-0.164***	-0.164***
×Reg	(0.0437)	(0.0449)	(0.0441)	(0.0437)	(0.0435)	(0.0436)	(0.0437)
Observations	14928	14242	14259	14712	14887	15120	14809
R^2	0.994	0.994	0.994	0.995	0.995	0.994	0.994
R^2 adj.	0.994	0.994	0.994	0.995	0.995	0.994	0.994

Table A.1.7: Leave-one-out analysis/3

	NOR	POL	SVK	ESP	SWE	CHE	TUR
Treated×Post	-0.165***	-0.158***	-0.163***	-0.166***	-0.167***	-0.167***	-0.160***
×Reg	(0.0435)	(0.0428)	(0.0436)	(0.0438)	(0.0442)	(0.0438)	(0.0435)
Observations	14220	14944	14994	14305	14460	14415	14955
R^2	0.994	0.995	0.994	0.994	0.994	0.994	0.994
R^2 adj.	0.994	0.995	0.994	0.994	0.994	0.994	0.994

Table A.1.8: Leave-one-out analysis/4

	UK	US
Treated×Post	-0.177***	-0.160***
×Reg	(0.0404)	(0.0428)
Observations	13977	14245
R^2	0.995	0.995
R^2 adj.	0.995	0.995

Table A.1.9: Intermediate Diff-in-diff for Germany and control countries.

	DiD Germany	*DiD controls*
	(1)	(2)
Post × Reg	-0.192***	0.006
	(0.030)	(0.017)
Post	0.000	-0.015
	(.)	(0.033)
Reg	-0.007	-0.015
	(0.011)	(0.011)
Ln prev	-0.353**	-0.006
	(0.140)	(0.019)
ln GDP pc	0.000	0.208***
	(.)	(0.065)
Years since first launch	-0.019***	-0.013***
	(0.007)	(0.003)
Constant	5.295***	-1.062
	(1.662)	(0.737)
Product, Time FE	Yes	Yes
Country FE		Yes
Observations	1087	14036
R^2	0.999	0.994
R^2 adj.	0.999	0.994

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

Table A.1.10: Sensitivity analysis on the number of observations for each product.

	Years considered			
	One year	Two year	Three year	Main
Treated × Post × Reg	-0.120**	-0.146***	-0.145***	-0.164***
	(0.047)	(0.035)	(0.039)	(0.044)
Treated × Post	-0.032	-0.037	-0.035	-0.020
	(0.032)	(0.033)	(0.033)	(0.031)
Treated × Reg	-0.000	-0.006	-0.018	-0.013
	(0.019)	(0.015)	(0.018)	(0.015)
Post × Reg	0.044**	0.036**	0.031	0.003
	(0.022)	(0.016)	(0.019)	(0.016)
Ln prev	-0.034	-0.032	-0.027	-0.008
	(0.021)	(0.020)	(0.019)	(0.020)
ln GDP pc	0.093	0.130	0.150	0.195***
	(0.105)	(0.110)	(0.106)	(0.063)
Years since first launch	-0.020*	-0.023**	-0.019**	-0.013***
	(0.010)	(0.010)	(0.008)	(0.003)
Constant	0.690	0.212	-0.093	-0.909
	(1.159)	(1.218)	(1.186)	(0.726)
Product, Year, Country FE	Yes	Yes	Yes	Yes
Observations	4322	7023	9174	15124
R^2	0.995	0.994	0.994	0.994
R^2 adj.	0.995	0.994	0.994	0.994

Standard errors in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Column 1 considers only one year of regulated observations, Column 2 considers only two years and Column 3 considers only three years of regulated observations. For regulated observations I intend those that fulfil the condition $Reg = 1$.

A.2 ERP with Discounts: Does it Pay to Keep a Secret?

A.2.1 Transparent Regime

The optimal profit is as shown in Equation A.1.

$$\Pi^T = \begin{cases} 1/4 - c/2 & \text{if} \quad v \leqslant \frac{1}{2+K} \quad \Leftrightarrow \quad d^T = 1 \\ \Pi^T(v,c) & \text{if} \quad \underline{v}_T < v < \frac{1}{2+K} \quad \Leftrightarrow \quad p_F^T = v \\ \Pi^T(v,K,c) & \text{if} \quad \frac{1}{2+K} < v < \underline{v}_T \\ \frac{(vK+1)^2}{4+4K} & \text{if} \quad v'_T \leqslant v \quad \Leftrightarrow \quad d^T = 0 \end{cases} \tag{A.1}$$

Where $\frac{\partial \Pi^T(v,K,c)}{\partial c} < 0$, $\frac{\partial \Pi^T(v,K,c)}{\partial v} > 0$ and $\frac{\partial \Pi^T(v,K,c)}{\partial K} > 0$ for any $\frac{1}{2+K} < v < v'_T$.

The Home Surplus is calculated as in Equation A.2.

$$S_H^T = \begin{cases} 1/8 & \text{if} \quad v \leqslant \frac{1}{2+K} \quad \Leftrightarrow \quad d^T = 1 \\ S_H^T(v,K,c) & \text{if} \quad \frac{1}{2+K} < v < v'_T \\ \frac{(1+(2-v)K)^2}{8(1+K)^2} & \text{if} \quad v'_T \leqslant v \quad \Leftrightarrow \quad d^T = 0 \end{cases} \tag{A.2}$$

The Home Surplus for $\frac{1}{2+K} < v < v'_T$ is increasing in K and increasing in c, whereas it is increasing in v for sufficiently low levels of c and it can have a global maximum in the interval for sufficiently high levels of c. For $v'_T \leqslant v$, instead, the optimal Home Surplus is always decreasing in v. The Foreign Surplus is shown in Equation A.3.

$$S_F^T = \begin{cases} 0 & \text{if} \quad v \leqslant \frac{1}{2+K} \quad \Leftrightarrow \quad d^T = 1 \\ S_F^T(v,K,c) & \text{if} \quad \frac{1}{2+K} < v < v'_T \\ \frac{(vK+2v-1)^2 K}{8(1+K)^2} & \text{if} \quad v'_T \leqslant v \quad \Leftrightarrow \quad d^T = 0 \end{cases} \tag{A.3}$$

Where, for $\frac{1}{2+K} < v < v'_T$, we have that $\frac{\partial S_F^T(v,K,c)}{\partial v} > 0$, $\frac{\partial S_F^T(v,K,c)}{\partial K} > 0$ and that $\frac{\partial S_F^T(v,K,c)}{\partial c} < 0$. When the level of v is above the no-delay threshold v'_T the sign of the partial derivatives remains the same, but the surplus would not depend on the delay and on the cost parameter c. Finally, the total Welfare is shown in Equation A.4.

$$W^T = \begin{cases} 3/8 - c/2 & \text{if} \quad v < v'_T \quad \Leftrightarrow \quad d^T = 1 \\ W^T(v,K,c) & \text{if} \quad \frac{1}{2+K} < v < v''_T \\ \frac{3K^2v^2 + 2K\left(2v^2 - v + 2\right) + 3}{8(1+K)} & \text{if} \quad v''_T < v \quad \Leftrightarrow \quad d^T = 0 \end{cases} \tag{A.4}$$

A.2.2 Opaque Regime

Optimal discount.

$$\mu^O = \begin{cases} 0 & \text{if} \quad v < v'_O \;\Leftrightarrow\; p_F^O = \frac{v}{1-\mu^O} \text{ and } d^O = 1 \\ \frac{(1-d^O)v^2K}{2(1-d^O)v^2K+b} & \text{if} \quad v'_O < v < \frac{1-\mu^O}{2+(1-\mu^O)^2K} \;\Leftrightarrow\; p_F^O = \frac{v}{1-\mu^O} \\ \frac{K(2p_F^O-v)(1-d^O)p_F^O}{2K(1-d^O)(p_F^O)^2+b} & \text{if} \quad \frac{1-\mu^O}{2+(1-\mu^O)^2K} < v < v''_O \\ \frac{p_F^O K(2p_F^O-v)}{2K(p_F^O)^2+b} & \text{if} \quad v''_O < v \Leftrightarrow\; d_F^O = 0 \end{cases} \tag{A.5}$$

A.3 Strategic Response to External Reference Pricing

A.3.1 Data Set and Descriptive Statistics

Based on latest surveys available (Gill et al., 2019; Kanavos et al., 2020; Vogler et al., 2019), ERP is used as the main criterion in Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Luxembourg, Malta, Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Russia and Turkey, while it is just a supporting criterion in Belgium, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Poland, Spain and Switzerland. Sweden and the UK do not make use of ERP. Denmark does make use of ERP, but only for hospital medicine, while it adopts free pricing for prescription medicine. All countries refer either to ex-factory prices (the majority) or to the pharmacy purchasing price (PPP). The basket of countries ranges from just one to the inclusion of all European countries. Finally, the most used price ceiling rules are the average price of the basket or the lowest price, or even a combination of the two, such as the average of the lowest 3 prices in the basket—adopted in Czech Republic, Greece, Norway and Slovakia. This is summarized in Table A.3.1.

Table A.3.1: ERP implementation in Europe: latest data available.

Country	*Criterion*	*Price*	*Medicine*	*Basket*	*Benchmark price*	*(1)*	*Revision frequency*	*(2)*
AUT	main	ex-factory	Reimb	26	average	no	ad hoc	all
BEL	supportive	ex-factory	All med	27	average	no	at launch only	in patent
BGR	main	ex-factory		17	minimum	no	Reimb. med.: every 6 m. Non reimb.: at launch only	all
HRV	main	PPP		3 out of 5	average	no	12	
CYP	main	PPP		4 out of 10	average	no	12	
CZE	main	ex-factory	Reimb/All med	18	average of 3 lowest	no	12	all
EST	main	ex-factory		3	Price cannot exceed the highest price in the basket	no	Outpatient: dep. on agreement. Inpatient: annually	in patent
FIN	supportive	PPP	Reimb	30	average	no	60	
FRA	supportive	ex-factory	Reimb/ innovative	4	Prices similar to basket and not lower than the lowest	no	Every 4–5 years	in patent
DEU	supportive	ex-factory	innovative	15	Weighted based on mkt size and PPP	yes	At launch and if new evidence available	in patent
GRC	main	ex-factory	Reim/all med	27	average of 3 lowest	no	Biannual in first 4 years	in patent
HUN	main	ex-factory	†	30	minimum	no	at launch only	in patent
ISL	main	PPP	4	average	no	24		
IRL	supportive	ex-factory	†	14	average	no	36	
ITA	supportive	ex-factory	Reim	25	average	no	ad hoc	in patent
LVA	supportive	ex-factory		7	third lowest price	no	24	all
LTU	supportive	ex-factory		27	average	no	12	
LUX	main	ex-factory	origin	minimum	no	12		
NLD	main	PPP	POM	4	average	no	6	
NOR	main	PPP	POM	9	average of 3 lowest	no	12	
POL	supportive	ex-factory	Reim	30	minimum	no	Every 2, 3, or 5 years)	all
ROU	main	ex-factory		12	minimum	no	12	all
SVK	main	ex-factory	Reim	27	average of 3 lowest	no	6	all
SVN	main	ex-factory		3	minimum	no	6	all
ESP	supportive	ex-factory	†	14	minimum	no	24	in patent
CHE	supportive	ex-factory	Reim	9	average	no	36	
RUS	main	PPP		12	minimum		At manufacturers' request	all
TUR	main	ex-factory	POM	5	minimum		n/a	in patent
SWE	no							
UK	no							

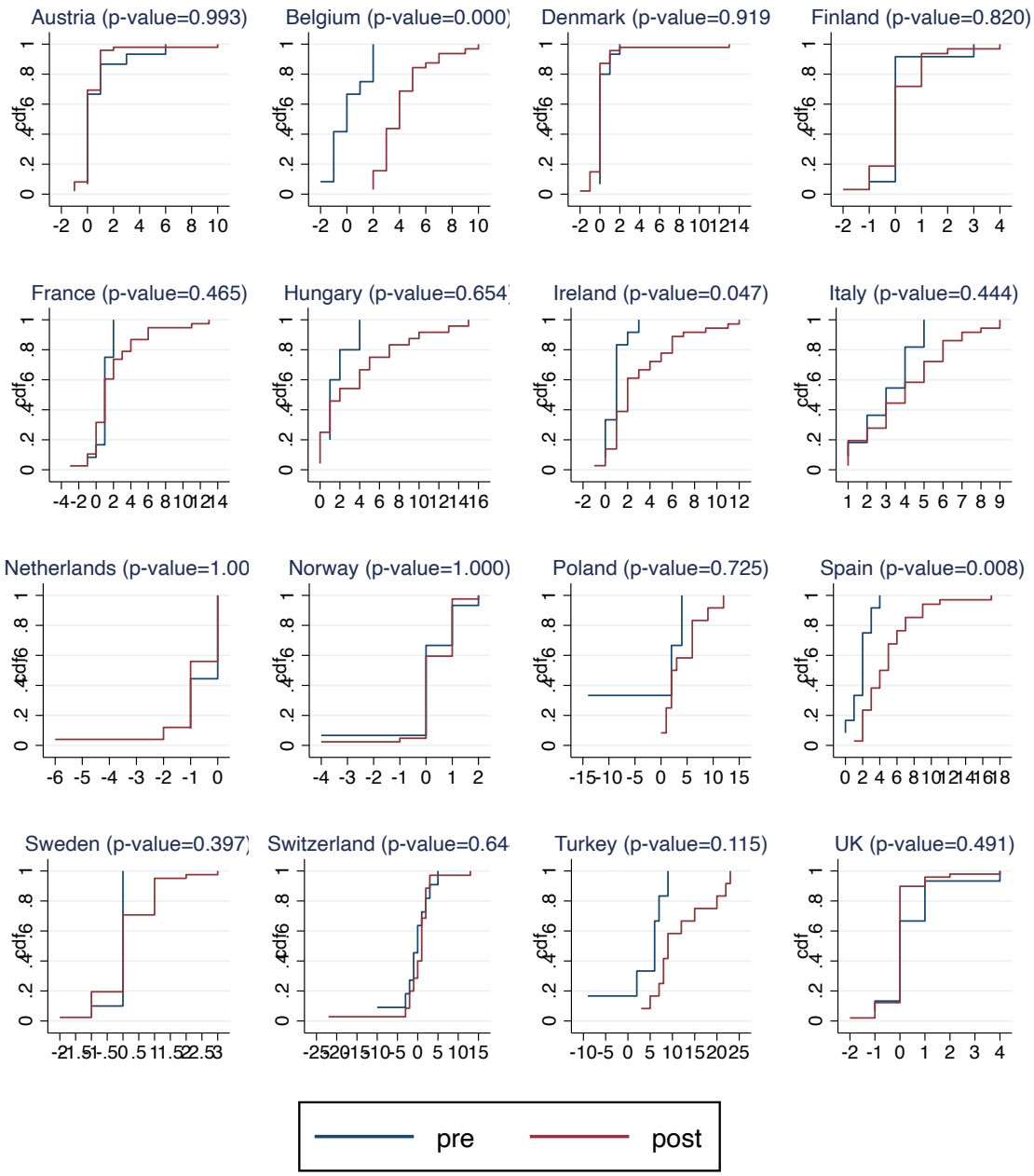
(1): presence of discounts. (2): Medicine patent status. Data from Gill et al. (2019), Kanavos et al. (2020), Vogler et al. (2019), Vogler et al. (2020).

Table A.3.2: Each product's descriptive statistics.

Product	*Avg.Price*	*St.Dev.*	*Product*	*Avg.Price*	*St.Dev.*	*Product*	*Avg.Price*	*St.Dev.*
Abraxane	2.97	0.52	Imbruvica	0.50	0.09	Stivarga	1.38	0.29
Adcetris	67.67	4.83	Imlygic	23.12	1.39	Sutent	3.59	0.20
Afinitor	12.25	1.07	Inlyta	15.56	1.77	Tafinlar	0.83	0.07
Arzerra	2.30	0.16	Iressa	0.31	0.04	Tagrisso	2.63	0.15
Atriance	1.34	0.10	Jakavi	3.99	0.59	Tasigna	0.18	0.02
Blincyto	72,221.14	10,345.48	Javlor	4.80	0.15	Teysuno	0.10	0.01
Bosulif	0.30	0.05	Jevtana	74.97	7.03	Torisel	28.66	3.22
Cabometyx	3.65	0.30	Kadcyla	18.30	1.44	Tyverb	0.07	0.01
Caprelsa	0.58	0.07	Keytruda	37.19	3.59	Vargatef	0.22	0.04
Cometriq	1.53	0.22	Kisplyx	6.55	0.88	Vectibix	4.25	0.42
Cotellic	4.62	0.33	Kyprolis	21.67	2.53	Venclyxto	0.55	0.04
Cyramza	6.13	0.77	Lenvima	6.46	0.79	Vidaza	3.54	0.41
Dacogen	23.93	3.83	Lonsurf	6.55	1.54	Votrient	0.13	0.02
Darzalex	4.88	0.79	Lynparza	0.24	0.03	Xalkori	0.38	0.03
Empliciti	3.97	0.62	Mekinist	112.83	15.82	Xaluprine	0.01	0.00
Erivedge	1.63	0.12	Nexavar	0.16	0.01	Yervoy	87.27	4.31
Farydak	36.28	7.92	Ninlaro	654.27	36.34	Yondelis	1,961.08	80.75
Gazyvaro	3.71	0.37	Opdivo	14.45	1.36	Zaltrap	3.84	0.39
Giotrif	1.56	0.24	Perjeta	6.91	0.42	Zelboraf	0.16	0.01
Halaven	439.16	31.71	Pixuvri	23.25	0.37	Zydelig	0.48	0.12
Ibrance	1.47	0.11	Portrazza	1.88	0.24	Zykadia	0.27	0.03
Iclusig	5.51	2.07	Sprycel	0.99	0.07			

A.3.2 Robustness Checks

Figure A.3.1: Results of the KS test for equality of cumulative distributions



For each country is reported the lag with respect to the German launches in quarter of a year, of products launched before 2011 (blue) and for products launched after 2011 (red).

Table A.3.3: Strategic effect with the exclusion of countries that failed the KS test

	No BE, IR, ES
Strategic	0.064**
	(0.030)
Ln prev	-0.010
	(0.025)
ln GDP pc	-0.780***
	(0.240)
Time since first launch (in years)	-0.055
	(0.043)
Exchange rate	0.438***
	(0.140)
Constant	9.590***
	(2.565)
Product FE	Yes
Country FE	Yes
Year FE	Yes
Observations	471
R^2 adj.	0.998

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