Strategic interaction in pharmaceutical price regulation: with or without U?

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Abstract

We study strategic interaction among countries in pharmaceutical price regulation resulting from innovation-related spillovers. In our theoretical model, regulators' pricing decisions affect welfare both directly and indirectly, via firms' R&D policies. We characterise two types of equilibrium, depending on whether countries price at, or above, the minimum level the industry is willing to accept to serve the market. The combination of these two equilibria may imply a U-shape relationship between countries' pharmaceutical prices and relative market size. We find support for this hypothesis, using data for 83 cancer drugs in 23 OECD countries. Our results contribute to the academic debate about the relationship between prices and market size, as well as the policy debate about using supranational procurement policies to lower prices. In particular, we show that joint procurement can lower or raise prices according to the sizes of the domestic markets which join to create a single purchasing authority.

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1 Introduction

According to the World Health Organisation, one of the biggest challenges facing health care systems worldwide is achieving fair pricing for pharmaceuticals, while at the same time ensuring

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long-term sustainability and access for patients (WHO, 2015a; OECD, 2018). In a large majority of countries, pharmaceutical prices are regulated and the academic literature has studied several aspects of the impact of such regulation on welfare. Most of this literature focuses on static efficiency considerations, i.e. the degree to which price regulation for pharmaceutical innovations secures access for patients in resource-constrained health care systems. However, since prices are a key determinant of profits made by the pharmaceutical industry, they also act as signals which can incentivise, or disincentivise, future investment and innovation in R&D (so-called 'dynamic efficiency' considerations).[1]

Since the results of innovation are potentially available on a global scale, a stronger incentive to invest in R&D that is created by one country's pricing and reimbursement policy can increase the probability that future innovations are available in other countries. This implies strategic dependency between national pricing regulations, creating a need to investigate them from an international perspective.[2]Despite these interdependencies, most of the existing literature has studied national pricing policies independently of one another. The aim of the present paper is to study theoretically strategic interaction among countries related to R&D incentives and to investigate empirically some of the theoretical predictions using an international data set of pharmaceutical pricing and reimbursement.

There are at least two policy-related aspects to our work. Firstly, it has been noted that the spillover effects of regulation on innovation create the potential for free-riding behaviour. In a review of the global pricing policies for pharmaceutical products, the OECD (2008, page 21) comments: 'countries whose policies restrict the prices pharmaceutical firms can charge for their products were, it was suggested, potentially free-riding on the rewards and incentives for innovation provided by others.'[3] A related matter concerns the merits of moving from single, national procurement authorities to larger, supranational authorities. For example, joint procurement of pharmaceutical products has been feasible in the European Union since 2014 and its merits have been widely debated.[4] Some joint procurement initiatives have been undertaken in the intervening years: the 27 member states of the EU adopted joint procurement, in preference to national procurement, for Covid-related medicines during the Covid-19 pandemic and the Beneluxa ini-

[1]See Kyle (2022) for a recent overview of the literature on incentives for pharmaceutical innovation.

[2]There are mechanisms other than innovation that imply a connection between pricing policies in different countries. The main example is probably the adoption of *external reference pricing*, whereby a country may refer to prices set in a certain group of countries in setting its own price. See, for example, Geng and Saggi (2017).

[3]For a recent discussion of the topic, see also the editorial by Hooper and Henderson (2022).

[4]In April 2014, the European Commission approved the Joint Procurement Agreement (JPA), which enables European countries to organise joint procurement procedures for medical countermeasures aimed at combating serious cross-border threats to health. More generally, joint procurement of any type of pharmaceutical product is feasible under European Directive 2014/24/EC.

tiative (beneluxa.org), a consortium involving Belgium, the Netherlands, Luxembourg, Austria and Ireland, aims to achieve sustainable access to medicines for its participating nations.

Despite these policy initiatives, the academic literature considering strategic interaction in price regulation and R&D incentives is rather limited and mainly focuses on the parallel trade of pharmaceutical products (Grossman and Lai, 2008; Bennato and Valletti, 2014; Brekke et al., 2015; Li and Maskus, 2006; Reisinger et al., 2019). However, the spillover effect of price regulation on innovation exists even in the absence of parallel trade. Among the contributions to address this idea, in their model of strategic profit regulation, Egan and Philipson (2013) show that profit provisions are strategic substitutes which are increasing in their respective market sizes. Similarly, Frech et al. (2023) model innovation as a global public good and find that, in equilibrium, larger countries bear a disproportionately large share of contributions. To the extent that profits and prices move in the same direction,[5] this prediction is in contrast to the arguments which suggest that joint procurement arrangements can lower prices as a result of increased monopsony power (Chown et al., 2019), as well as with some empirical evidence on the matter (Lakdawalla and Yin, 2015; Dubois et al., 2021).

In this paper, we propose a theoretical model of pharmaceutical price regulation which addresses this gap in the literature and which informs the debate about the aforementioned policy questions. In our model, regulators simultaneously set prices to maximise their respective domestic social welfare functions, allowing for the fact that pricing decisions affect consumer surplus directly as well as indirectly, because they affect private firms' R&D decisions and therefore patient health. We study the properties of two types of Nash equilibria: 1. those where both countries set their prices above the minimum level that the firm is willing to accept in order to serve their domestic markets and 2. those where the minimum price level is binding for one of the two countries. Comparative static analysis shows that the impact of country characteristics on equilibrium price is different in the two equilibria. In particular, the size of the national market relative to the global market is a key determinant of both the type of equilibrium and, given the type of equilibrium, the optimal price. These results are suggestive of a U-shape relationship between equilibrium price and relative market size. The key mechanism underlying this result is that, other things being equal, the within country impact, at the patient level, of a price increase is the same, no matter whether the country is large or small. However, the impact on international profits, and hence on incentives to invest in R&D, of that price increase will be much larger if implemented in a large country. This makes relative market size a crucial determinant of a country's strategic position. Using a data set from the Pricing Insights IMS Health database, which

[5] For a discussion of this point, see Section 3.2.1 of Egan and Philipson (2013).

includes the prices of 83 branded cancer drugs between 2007 and 2017 in 23 OECD countries, we find evidence which supports the prediction of a U-shaped relationship between pharmaceutical prices and relative market size.

Our results reconcile the aforementioned competing views in the literature concerning the sign of the relationship between pharmaceutical prices and market size. They suggest that both views may be relevant, according to whether a country is small or large. Consequently, our work has important implications for the policy debate concerning the merging of procurement authorities to contain prices. A U-shaped relationship between prices and market size implies that very small countries have the largest potential to reduce prices through joint procurement. However, according to our results, a very large procurement authority, such as a single EU agency, cannot guarantee that all countries would achieve a reduction in prices.

Section 2 reviews the background literature. Section 3 presents our two-country model of strategic interaction in pharmaceutical price regulation and innovation. In section 4 we obtain best responses, conduct comparative static analyses and study optimal investment and pricing policies. We present our empirical analysis in section 5. Section 6 discusses our results and concludes.

2 Background literature

This paper is related to at least three separate strands of literature. First, there is a theoretical and empirical literature which studies strategic interaction among policy makers in a number of fields where spillover effects occur. The best known field is probably environmental policies with global impacts, such as those designed to control the emission of pollutants (Murdoch and Sandler, 1997). Another is taxation of capital income in the presence of capital mobility. In this case, a reduction in the tax rate in one country implies a negative externality for other countries, because it shrinks their tax bases (see, for example, the seminal paper by Zodrow and Mieszkowski, 1986). Devereux et al. (2008) provide empirical evidence supporting the theoretical prediction of strategic interaction in this area. Another field is that of tariff policies, owing to the negative externality associated with a tariff set in one country on the exporter's terms of trade (Beshkar et al., 2015). Concerning health related innovation, Kyle et al. (2017) investigate free riding in public funding of medical research using data on funding for infectious and parasitic diseases from the US National Institutes of Health between 2007 and 2014. The authors find that a 10% increase in US government research funding for one disease is associated with a 2 to 3% reduction in funding for the same disease by another government in the following year. Egan and

Philipson (2013) focus on the growth of the global market in health technology by proposing a theoretical model of strategic interaction in profit regulation. Based on their empirical findings, they conclude that a growth in the market size of BRICS countries may reduce world returns from pharmaceutical innovation owing to increased free riding in non-BRICS countries.

A second strand of literature concerns the international dimension of intellectual property protection. This is particularly relevant for the pharmaceutical market because of the role played by innovation and the fact that pharmaceutical companies operate on a global scale. There is also scope for strategic interaction in this area, because stronger protection of intellectual property in one country may provide incentives to invest in R&D in that country, and this investment may benefit other countries. Grossman and Lai (2004) study strategic interaction in the definition of patent policies between a 'Northern' country, with comparatively large R&D productivity, and a 'Southern' country. They show that, in a noncooperative equilibrium, patent protection is stronger where R&D capacity and market size are greater. Another question in this literature concerns the welfare implications of parallel trade. The dominant view is that parallel trade weakens incentives to invest in R&D, by reducing profits in countries where patents have yet to expire (Barfield and Groombridge, 1998, 1999; Danzon, 1998; Danzon and Towse, 2003; Li and Maskus, 2006; Reisinger et al., 2019). Grossman and Lai (2008) challenge this view by showing that parallel trade may lead to greater investment in R&D. Crucial for this result is the impact of parallel trade on optimal price regulation. The authors also find that optimal pricing polices depend on the relative size of the market and that the relationship between relative market size and optimal price is not strictly monotonic. Key differences between this literature and our analysis are that we focus on pricing policies in situations where intellectual property is protected and that our countries differ along a number of dimensions, but not in R&D productivity. This is because the debate on free-riding in pharmaceutical price settings has mainly concerned 'Northern' countries, using Grossman and Lai's terminology.

Finally, our work is related to the empirical literature studying the determinants of drug prices.[6] Most relevant for us are those studies that adopt a comparative approach (see, for example, Cabrales and Jiménez-Martín, 2013; Kanavos and Vandoros, 2011; Von der Schulenburg et al., 2011; Kyle and Qian, 2014). Covariates typically considered in these analyses include the age of the drug, its therapeutic advance, patent status, presence and number of (generic) competitors, GDP per capita, the country's level of health expenditure and the level of regulation. Several other contributions study the determinants of prices within countries (see, among others, Lu and Comanor (1998) for the United States, Ekelund and Persson (2003) for Sweden and,

[6] See OECD (2008, Chapter 2) and Daalen et al. (2021) for an overview.

separately, for the United States, Benda et al. (2004) for Canada, and Puig-Junoy and González López-Valcárcel (2014) for Spain). Where market size has been considered among the potential determinants of pharmaceutical prices, only linear relationships have been modelled. In some cases, it has been included alongside other explanatory variables, with no clear expectation on the sign of its coefficient. This is the case of Kyle and Qian (2014), Puig-Junoy and González López-Valcárcel (2014) and Helble and Aizawa (2017), none of which found a statistically significant relationship between the two variables. The theoretical analysis of Egan and Philipson (2013) referred to above predicts a positive relationship between profits made in a country and the country's market size. In their empirical analysis, the authors use an index of pharmaceutical prices as the dependent variable and they find a positive, non-significant association for some specifications of the empirical model and a negative, significant association for others. Using indices of pharmaceutical prices at the country level that are sourced from Mulcahy et al. (2021), and using GDP to proxy the size of the economy, Frech et al. (2023) also present an empirical investigation of cross-country differences. The authors find that estimated elasticities of price with respect to GDP exceed unity, which they interpret as supporting the idea that smaller countries are more likely to free-ride on larger ones.

3 The model

We model two countries, A and B, which are assumed to comprise the global market, in which a single profit-maximising firm may sell a new drug. In each country, there is an authority responsible for regulating the prices of new drugs that are approved for commercialisation ('the regulator'). Patient-level marginal willingness to pay (MWTP) for the drug in country c, $c \in \{A, B\}$, is given by the linear inverse demand function:

$$\text{MWTP}^c(q^c) = \kappa^c \delta(I) - b^c q^c. \tag{1}$$

The quantity q^c may be interpreted as the average level of consumption of the drug by each of N^c patients eligible to receive it in country c.[7] I is the level of R&D investment, a choice variable for the firm. An increase in I is assumed to improve the effectiveness of the drug, implying a

[7] If all patients in country c are identical, the negative slope of the MWTP function results from the standard assumption of decreasing marginal utility of consumption. With heterogeneous patients, a more realistic interpretation is that patients may or may not consume a fixed quantity of the drug, this quantity being determined by clinical guidance relating to what is the best average dosage (ignoring second-order effects). In this case, the slope of the MWTP function is still negative because an increase in q^c means that the drug is extended to sub-groups of patients for whom it is comparatively less effective.

positive impact on MWTP via the function δ, for which it is assumed $\delta(0) = 0$, and that the derivatives have the following properties: $\delta_I > 0, \delta_{II} < 0$ and $\lim_{I \to 0} \delta_I = \infty$. For the types of increasing and strictly concave functions typically employed in economics, this also implies $\delta_{III} > 0$. The parameter κ^c accounts for cross-country differences in willingness to pay due, for example, to differences in preferences or per capita income. b^c is the slope coefficient.

If the drug is introduced to market c, we assume that the quantity consumed equates the reimbursement price chosen by the regulator, p^c, with MWTP^c. This assumption is compatible with a system in which patients are fully insured and the regulator enforces an efficient level of consumption (e.g. by gate-keeping), or systems in which there is no health insurance and drug expenditure is fully out-of-pocket. The individual demand function for country c is then obtained by rearranging Eq. (1):

$$q^c = \frac{\kappa^c \delta(I) - p^c}{b^c}. \tag{2}$$

3.1 The firm

The firm takes the prices p^A and p^B chosen by the regulators as given and chooses I to maximise profit from sales in the global market:

$$\Pi(I; p^A, p^B, \boldsymbol{\beta}) = N \left[\mathbf{1}_{p^A \geq r^A} [n^A (p^A - m) q^A - C^A] + \mathbf{1}_{p^B \geq r^B} [(1 - n^A)(p^B - m) q^B - C^B] \right] - I, \tag{3}$$

where m and C^c are, respectively, the marginal cost of production and the fixed cost of entering the market of country c (see, for example, Bennato and Valletti, 2014); $N = N^A + N^B$ is the size of the global population eligible to receive the treatment, normalised to 1 in what follows, and $n^A = N^A/N$ is the relative size of country A's market. The indicator function $\mathbf{1}$ accounts for the fact that the new drug is marketed in country c if and only if p^c exceeds a reservation price $r^c \geq m$, where r^c is simultaneously defined in both countries as the minimum price that allows net revenues to be non-negative in country c. Allowing for the possibility that the firm decides not to enter the market is consistent with the existing evidence that even essential pharmaceuticals may not be available in some markets (Hogerzeil and Mirza, 2011). This occurs despite the fact that the marginal cost of production is typically almost negligible for most pharmaceutical products (Newhouse, 2004; Barton and Emanuel, 2005). Finally, $\boldsymbol{\beta} \stackrel{\text{def}}{=} (n^A, m, \kappa^A, \kappa^B, r^A, r^B, b^A, b^B)$.

3.2 Regulators

The regulators in countries A and B are responsible for setting prices with the objective of maximising their own country's welfare. Unlike in Egan and Philipson (2013) and Frech et al. (2023), the decision variable is the price, which allows us to explicitly separate the role of price and sale volumes as determinants of profit. Price setting is assumed to take place simultaneously and non-cooperatively. Welfare is a weighted average of internal consumer surplus and the firm's profit accruing to that country:

$$W^A(p^A; p^B, \boldsymbol{\beta}) = \alpha^A \text{CS}^A + (1-\alpha^A)\lambda\Pi, \tag{4a}$$

$$W^B(p^B; p^A, \boldsymbol{\beta}) = \alpha^B \text{CS}^B + (1-\alpha^B)(1-\lambda)\Pi, \tag{4b}$$

where $\text{CS}^c = N^c \int_{p^c}^{\kappa^c\delta(I)} q^c(p^c)\text{d}p^c = \frac{N^c}{2b^c}\left[\kappa^c\delta(I) - p^c\right]^2$ is consumer surplus, λ is the fraction of global firm profit accruing to country A and α^c and $(1-\alpha^c)$, $0 \leq \alpha^c \leq 1$, are, respectively, the weights placed on consumer surplus and profits.

Allowing social welfare to depend on the firm's profit accounts for the fact that, for regulators of countries with a comparatively large pharmaceutical industry, setting comparatively high prices may be an indirect way of subsidising the domestic industry (Wagner and McCarthy, 2004; Espin et al., 2011; Frech et al., 2023).

3.3 Timing

The timing in the model is assumed to be as follows: in the first stage, regulators set prices (as, e.g., in Grossman and Lai 2004) to which they can commit (Grossman and Lai, 2008).[8] In the second stage, knowing the prices set in the two countries, the firm chooses its optimal level of R&D investment.

4 Optimal investment and pricing policies

We solve the model backwards, starting by establishing the optimal investment policy of the firm. This allows us to establish the regulators' best responses and the Nash equilibrium which, in turn, are used to carry out comparative statics analyses and derive testable hypotheses. In doing this,

[8] It may seem unrealistic that regulators set prices before the firm invests in R&D. However, lacking commitment, regulators would be tempted to price at marginal cost of production once R&D costs are sunk. Foreseeing this, firms would decide not to invest in R&D. Hence, commitment in this context can be justified by a reputation argument. See Grossman and Lai (2008) for a discussion of this point.

we restrict our attention to stationary equilibria in which both countries adopt the new drug, so that $p^c \geq r^c$ in both countries.

4.1 The firm's optimal policy

In order to define the profit maximizing level of investment, the firm solves:

$$\Pi^*(I; p^A, p^B, \boldsymbol{\beta}) = \max_{I>0} \Pi(I; p^A, p^B, \boldsymbol{\beta}).$$

The first order necessary condition for the optimal investment policy, $I^*(p^A, p^B, \boldsymbol{\beta}) > 0$, is:

$$\frac{\partial \delta}{\partial I} = \frac{b^A b^B}{[n^A(p^A - m)\kappa^A b^B + (1 - n^A)(p^B - m)\kappa^B b^A]}. \tag{5}$$

Given the assumptions $\lim_{I \to 0} \delta_I = \infty$ and $\delta_{II} < 0$, the second order condition is satisfied at a value of $I^* > 0$. Concavity of $\delta(I)$ implies that an increase in either p^c or κ^c both have a positive impact on I^*. Moreover:

$$\frac{\mathrm{d}I^*}{\mathrm{d}n^A} \gtreqless 0 \quad \text{if} \quad (p^A - m)\kappa^A b^B \gtreqless (p^B - m)\kappa^B b^A. \tag{6}$$

Having characterized the optimal investment policy, it is convenient to observe that, for a given price combination (p^A, p^B), the firm's optimal investment policy, as defined by Eq. (5), fixes δ and therefore the position of the MWTP function in both countries. Therefore, for a given value of p^A, there is just one value of q^A which is consistent with both the firm's optimal investment decision and the rule equating price and MWTP. We define this as the 'feasible quantity function' $\hat{q}^A$:

$$\hat{q}^A(p^A; p^B, \boldsymbol{\beta}) = \frac{\kappa^A \delta(I^*(p^A; p^B, \boldsymbol{\beta})) - p^A}{b^A}, \tag{7}$$

which is helpful for the following analysis of the optimal choice of p^A.

The firms' reservation prices, r^A and r^B, are determined to be the minimum values of p^A and p^B that ensure non-negative net revenues in each market. Of particular interest in this paper is the dependency of prices on relative market size. The following proposition summarises a first result on this relationship:[9]

Proposition 1. *For sufficiently small values of* n^A, $\partial r^A / \partial n^A < 0$. *Irrespective of the value of* n^A,

[9] For notational simplicity, in what follows, we use subscripts to denote partial derivatives of the welfare function.

a sufficient condition to ensure $\partial r^A/\partial n^A < 0$ *is that,* ceteris paribus*, net revenues are increasing in* n^A*, i.e.* $\Pi^A_{n^A} > 0$ *and* $\Pi^B_{n^A} < 0$.

Proof. See Appendix A.1.

Intuitively, the reason why, under reasonable conditions, the reservation price is decreasing in the own relative market size is that the opportunity cost for the industry of not serving a market is larger the larger its size.

4.2 The regulator's optimal price

The two regulators face the same problem: to choose the optimal price in their own country, knowing that the other regulator shall simultaneously do likewise, and knowing that the firm's optimal investment policy is defined by Eq. (5). Here we consider the problem faced by the regulator in country A. A similar approach applies for the regulator in country B.

The regulator in country A solves:

$$W^{A*}(p^A; p^B, \boldsymbol{\beta}) = \max_{p^A \geq r^A} W^A(p^A, I^*(p^A; p^B, \boldsymbol{\beta}); \boldsymbol{\beta}).$$

Exploiting the properties of the Envelope theorem, the solution to the maximization of W^A with respect to p^A satisfies the following conditions:

$$\begin{aligned} W^A_{p^A} = n^A \left[\alpha^A b^A \hat{q}^A \frac{\partial \hat{q}^A}{\partial p^A} + (1-\alpha^A)\lambda \left(\hat{q}^A + \frac{m - p^A}{b^A} \right) \right] \leq 0, \\ p^A - r^A \geq 0, \quad (p^A - r^A) W^A_{p^A} = 0. \end{aligned} \tag{8}$$

If $\alpha^A = 1$, meaning that only consumer surplus matters for welfare, Eq. (8) shows that, when an interior solution exists, welfare maximization is equivalent to maximizing $\hat{q}^A$. For what follows, we introduce the assumption that $\hat{q}^A(\cdot)$ is strictly concave in p^A. This means that, for an interior solution, the condition $\partial \hat{q}^A/\partial p^A = 0$ identifies the value of p^A that maximises CS. The characteristics of the function $\delta(I)$ under which this holds are discussed in Appendix A.2. If $\alpha^A = 0$, meaning that only profits matter for welfare, marginal revenue equals marginal cost when an interior solution exists.

Figure 1 provides a graphical illustration. Values of p^A on the vertical axis are mapped to unique values $I^*(p^A; p^B, \boldsymbol{\beta})$ (see Eq. (5)), which in turn define δ and hence the MWTP functions. The corresponding feasible quantity function, $\hat{q}^A(p^A; p^B, \boldsymbol{\beta})$, results from the rule equating price

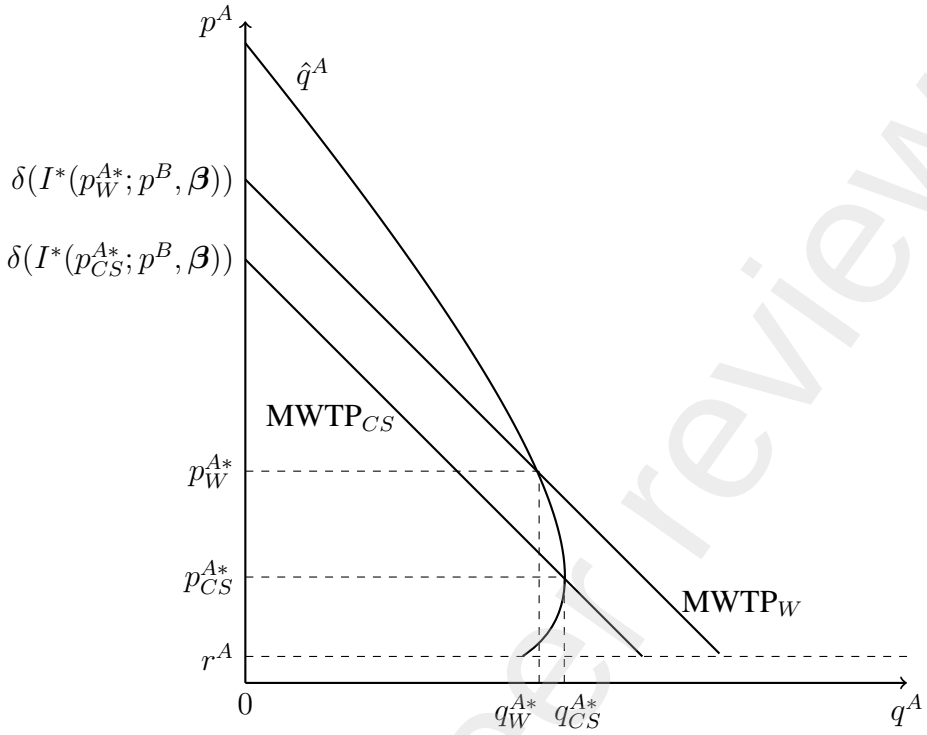


Figure 1: Feasible quantity function $\hat{q}^A$ and two inverse demand functions showing optimal levels q^{A*} resulting from the optimal choice of price p^{A*}. MWTP$_{CS}$ results from the solution to the regulator's problem when only consumer surplus matters for welfare (giving $(q_{CS}^{A*}, p_{CS}^{A*})$). MWTP$_W$ results from the solution to the regulator's problem when both consumer surplus and profit matter for welfare (giving (q_W^{A*}, p_W^{A*})).

and MWTP. The figure shows $\hat{q}^A$ as a function of p^A which, according to the assumption that was introduced above, is strictly concave. It also shows two possible optima for the regulator in country A, together with the corresponding MWTP functions: $(q_{CS}^{A*}, p_{CS}^{A*})$ when only consumer surplus matters for welfare ($\alpha = 1$) and (q_W^{A*}, p_W^{A*}) for a value of α, $0 < \alpha < 1$, such that both consumer surplus and profits matter. In the event that the first line of Eq. (8) is negative when $p^A = r^A$, the corner solution $p^{A*} = r^A$ results.

Finally, we note that, at an interior solution, the first line of Eq. (8) may be recast as an adjusted Lerner's Index:

$$\frac{p^{A*} - m}{p^{A*}} = -\frac{1}{\epsilon^A \lambda}\left[\lambda + \frac{\alpha^A}{1-\alpha^A}\left(-1 + \kappa^A \frac{\partial \delta}{\partial I^*}\frac{\partial I^*}{\partial p^A}\right)\right]. \tag{9}$$

Compared with Lerner's Index for the standard monopolist's problem, Eq. (9) has an extra term. This accounts for the weighted adjustment to mark-up over marginal cost that is made as a result

of the welfare function including consumer surplus rather than solely profit. The term accounts for the marginal impact of p^A on consumer surplus via the direct price effect (-1) and the indirect impact on the MWTP function ($\kappa^A(\partial\delta/\partial I^*)(\partial I^*/\partial p^A)$) via the R&D incentive.

4.3 Best responses

When $W^A_{p^A} = 0$ at a maximising value of p^A (so that $W^A_{p^Ap^A} < 0$), the implicit function theorem may be used to show that, for any parameter θ, $\mathrm{d}p^{A*}/\mathrm{d}\theta = -W^A_{p^A\theta}/W^A_{p^Ap^A}$. Hence, for the parameters p^B, n^A and κ^A, for an interior solution, the sign of $\mathrm{d}p^{A*}/\mathrm{d}\theta$ is the same as the sign of the following expression:

$$\frac{\partial\hat{q}^A}{\partial\theta}\left[\alpha^A b^A\frac{\partial\hat{q}^A}{\partial p^A} + (1-\alpha^A)\lambda\right] + \alpha^A b^A\hat{q}^A\frac{\partial^2\hat{q}^A}{\partial p^A\partial\theta}, \tag{10}$$

where $\theta \in \{p^B, n^A, \kappa^A\}$. When $\theta = p^B$, Eq. (10) may be used to characterise the best response $p^{A*}(p^B)$. If only consumer surplus matters for welfare ($\alpha^A = 1$), we note that, for an interior solution, it must be the case that $\partial\hat{q}^A/\partial p^A = 0$ (refer to Eq. (8)). In this case, the slope of country A's best response function has a closed form solution, with a similar argument holding for country B when $\alpha^B = 1$:

$$\frac{\mathrm{d}p^{A*}}{\mathrm{d}p^B} = -\frac{\kappa^B(1-n^A)b^A}{\kappa^A n^A b^B}; \quad \frac{\mathrm{d}p^{B*}}{\mathrm{d}p^A} = -\frac{\kappa^A n^A b^B}{\kappa^B(1-n^A)b^A}. \tag{11}$$

So, for this special case, the slopes of the best response functions depend only on the relative sizes of the market, weighted by the ratios of the κs and bs. The functions are downward-sloping and prices are strategic substitutes. If both consumer surplus and profits matter for welfare ($0 < \alpha^A < 1$), the contribution to welfare of the profit component is positive because $\partial\hat{q}^A/\partial p^B > 0$ (refer again to Eq. (8)). Hence, for α^A sufficiently close to zero, prices are strategic complements.

In principle, therefore, the best responses may involve a positive or negative relationship between the optimal price set in one country and price in the other, and may be non monotonic. We assume that the weight on consumer surplus within each country's welfare function is sufficiently large to make prices strategic substitutes.

Consider now the impact of changes in some of the main parameters of interest on $p^{A*}(p^B)$. These results will be useful in section 4.4, where we consider the comparative statics of equilibrium price levels. It is again useful to start by assuming that $\alpha^A = 1$, so that only consumer surplus matters. In this special case, as already noted, the condition for an interior optimal price is $\partial\hat{q}^A/\partial p^A = 0$, so that the sign of Eq. (10) is the same as the sign of $\partial^2\hat{q}^A/\partial p^A\partial\theta$. For $\theta = n^A$,

the following results apply for an interior solution:

Proposition 2. *If only consumer surplus matters for country A's welfare and the marginal impact of p^A on the feasible quantity $\hat{q}^A$ is increasing in its relative market size, the optimal price $p^{A*}(p^B) > r^A$ is increasing in country A's relative market size.*

Proof. See Appendix A.3.

Corollary 1. *When only consumer surplus matters for welfare in both countries, the sign of $\partial p^{B*}/\partial n^A$ is the opposite to that of $\partial p^{A*}/\partial n^A$.*

Proof. Holding the total size of the market fixed, an increase in n^A implies a reduction in the size of country B's market. Therefore a similar argument to that used for the proof of Proposition 2 may be used to prove Corollary 1.

Intuitively, the condition of Proposition 2 ($\partial^2 \hat{q}^A/\partial p^A \partial n^A > 0$), namely that the marginal impact of p^A on the feasible quantity $\hat{q}^A$ is increasing in n^A, means that the upward shift of the MWTP function implied by an increase in the price p^A is greater, the greater the relative market size n^A. This may happen because, other things being equal, an increase in price strengthens the incentive to invest in R&D more when it occurs in a country with a comparatively large relative market size (refer to Eq. (5)). Whether the condition is satisfied or not depends on the functional form of $\delta(I)$. The conditions under which Proposition 2 holds are satisfied by some common functional forms of $\delta(I)$ (see Appendix A.3).

When $\alpha^A < 1$, so that both consumer surplus and profits matter for welfare, as long as the weight on consumer surplus in the regulator's objective function is sufficiently close to 1, an increase in n^A shifts country A's best response upwards.[10] Using similar arguments to those in Corollary 1, the effect of changing n^A on p^{B*} is the opposite to that of the effect on p^{A*}.

Now consider the comparative statics results for κ^A. Letting $\theta = \kappa^A$ in Eq. (10), similar arguments may be used to observe that, when the weight on consumer surplus in the welfare function is sufficiently large, the sign of $\mathrm{d}p^{A*}/\mathrm{d}\kappa^A$ is driven by the sign of the term $\partial^2 \hat{q}^A/\partial p^A \partial \kappa^A$. The following result applies for an interior solution:

Proposition 3. *If only consumer surplus matters for country A's welfare, the optimal price $p^{A*}(p^B)$ is increasing in κ^A.*

[10] With $\alpha^A < 1$, we can no longer eliminate the first two terms in Eq. (10) when establishing the sign of $\partial p^{A*}/\partial n^A$. The sign of $\partial \hat{q}^A/\partial n^A$ is ambiguous because it is the same as the sign of $\partial I^*/\partial n^A$, and this may be positive or negative (refer to Eq. (6)). The sign of $\partial \hat{q}^A/\partial p^A$ is also ambiguous, since it depends on whether p^{A*} lies above or below the consumer surplus maximising price (refer to Figure 1).

Proof. See Appendix A.4.

Finally, we comment on the impact of the fraction of the global profit accruing to countries A and B, λ and $1-\lambda$ respectively, on the best responses, when both CS and profits matter. Given that an increase in λ corresponds to an increase in the weight on the profit component of the welfare function for country A, it follows that an increase in λ (respectively, $1-\lambda$) implies an increase in $p^{A*}(p^B)$ (respectively, $p^{B*}(p^A)$), as long as the profit maximizing price exceeds the consumer surplus maximizing price (refer to Eq. (8)).

4.4 Equilibria

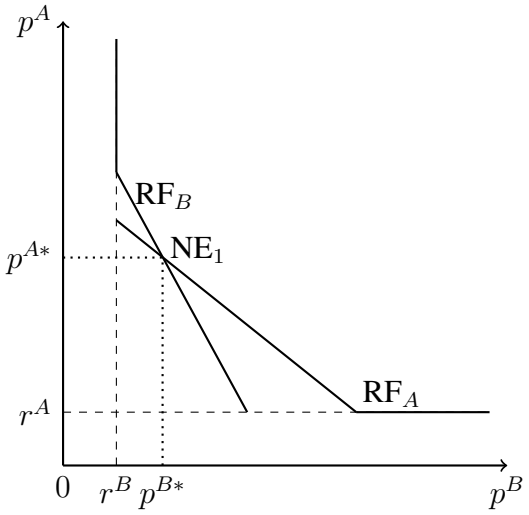
With our focus on negatively sloped best response functions in mind, we consider unique, stable, Nash equilibria in pure strategies, under our assumption that both countries adopt. Under these assumptions, two types of equilibria exist, as illustrated in Figure 2. Figure 2a shows a standard Nash equilibrium with interior solutions, meaning that the equilibrium values p^{A*} and p^{B*} are strictly greater than their respective reservation prices. Figure 2b shows a Nash equilibrium involving a corner solution for country A ($p^{A*} = r^A$), owing to the fact that A's best response function lies below that of B over the whole relevant domain. This type of equilibrium is also relevant in other fields, such as environmental economics, in games where regulators strategically interact in setting their emission levels (see, for example, Finus, 2001).

Consider now the comparative statics for an interior Nash equilibrium when prices are strategic substitutes. The following proposition summarises the impact of a change in the main parameter of interest for our analysis, i.e. the relative size of the market, n^A:

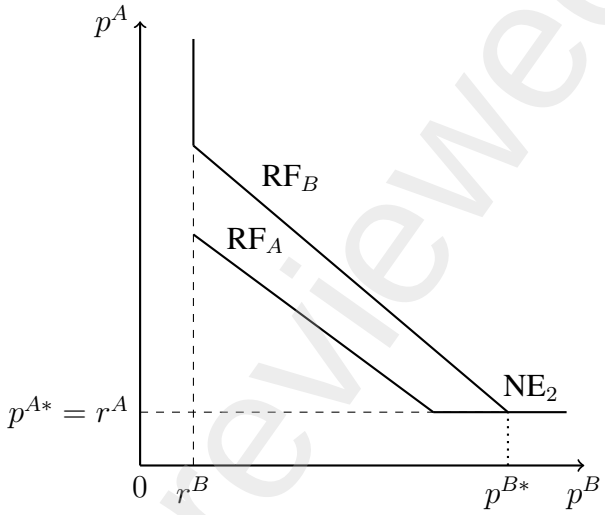
Proposition 4. *When prices are strategic substitutes, the conditions of Proposition 2 are sufficient to imply that an increase (decrease) in n^A implies an increase (decrease) in country A's price in a stable equilibrium involving an interior solution.*

Proof: See Appendix A.5.

Given the difference between equilibria involving an interior and a corner solution, it is interesting to investigate the role of the model parameters in determining whether the relevant Nash equilibrium is of one type or the other. The comparative statics analysis of section 4.3 has shown that several parameters affect the position of the best response functions and hence potentially also affect the relevant type of equilibrium. The impact of n^A on the type of equilibrium is described in the following Corollary.



(a) Downward-sloping, intersecting best response functions showing interior solution (NE$_1$).



(b) Non-crossing best response functions showing a corner solution for country A (NE$_2$).

Figure 2: Reaction functions and Nash equilibria (linear functions are drawn for illustrative purposes).

Corollary 2. *If the conditions under which $\partial p^{A*}/\partial n^A > 0$ hold, and the initial equilibrium involves a corner solution for country A ($p^{A*} = r^A$), then an increase in the relative size of country A's market from n^A to $n^A + \epsilon$, $\epsilon > 0$, keeping the other parameters fixed, may lead to a new equilibrium with interior solution $p^{A*} > r^A$.*

The corollary follows from the analysis of the dependency of the position of the best response functions on n^A. In particular, we showed in Proposition 2 that, under reasonable assumptions, an increase in n^A shifts country A's best response function upwards and B's downwards. Therefore, if A's best response function lies below B's initially, the increase in n^A may imply a shift from an equilibrium where $p^{A*} = r^A$ to one with interior solutions. The negative relationship between r^A and n^A that was discussed in section 4.1 reinforces this tendency. This situation is illustrated with a simulation in Appendix A.6.

4.5 The U-shaped relationship between equilibrium prices and relative market size

The preceding analysis showed that two types of Nash equilibria can occur in our setting. In one, the best response functions do not intersect, so that the reservation price is binding for one country and the other country responds optimally. In the other NE, both equilibrium prices are

strictly greater than the reservation prices. Both types of equilibria entail some form of free-riding. In the former, countries with comparatively low market shares exploit their strategic position to price as low as they can. In the latter, the equilibrium results from the intersection of negatively sloped best responses, meaning that prices are strategic substitutes.

Under the conditions of Proposition 2, the lower is country A's relative market size n^A, the lower is its best response function. Hence, other things being equal, a sufficiently small value of n^A leads to a corner solution NE, in which country A's price equals its reservation price. According to Proposition 1, under plausible assumptions, r^A is decreasing in n^A. Hence, conditional on the NE involving a corner solution, prices set by the country for which the reservation price is binding are decreasing in that country's relative market size.

On the other hand, a sufficiently large value of n^A leads to an interior solution NE, in which the best response functions intersect and country A's price is strictly greater than r^A. This means that an increase in n^A can imply a move from a corner to an interior NE (Corollary 2). In this type of equilibrium, country A's equilibrium price p^{A*} is increasing in n^A (by Proposition 4).[11]

In summary, equilibrium prices are predicted to be decreasing in the relative size of the market when the reservation price is binding, which occurs for low values of n^A, and they are predicted to be increasing in the relative size of the market for interior solution Nash equilibria, which result when n^A is large. The theory therefore predicts a U-shaped profile for Nash equilibria prices as a function of relative market size. Our empirical analysis focuses on testing this prediction.

5 Empirical analysis

In this section we investigate empirically the hypothesis that there exists a U-shaped relationship between countries' Nash equilibrium drug prices and their relative market sizes. In line with a number of other studies of pharmaceutical pricing and reimbursement (Danzon and Chao, 2000b; Von der Schulenburg et al., 2011; Cabrales and Jiménez-Martín, 2013; Kyle and Qian, 2014), we use data from the Pricing Insights IMS Health database for our analysis.[12] IMS Health price data are probably the best data available for comparisons among a large number of countries. They have the added advantage of including official mandatory rebates, which reduces the risk of measurement error in prices. Although our data account for mandatory rebates, they do not

[11] Note that a further increase in n^A might lead to a situation where the other country prices at r^B. Even in this case, p^{A*} is increasing in n^A.

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

account for confidential discounts.[13]that studied empirically the mechanisms related to strategic interaction. This dataset

Our data set comprises cancer drugs that received European Medicines Agency (EMA) authorisation between January 1995, when the EMA was established, and 30th March 2017, and which are sold in OECD countries. We focus on OECD countries because they make up a large share of the global market and they tend to use each other's prices as a reference point (WHO, 2015b; Espin et al., 2014). We focus on cancer drugs because, together with statins, they represent the two largest therapeutic classes in terms of sales value (OECD, 2008) and 22% of prescription drug sales in 2026 are forecast to come from oncology treatments (EvaluatePharma, 2021). Further, in recent years, this therapeutic area has been characterised by a number of innovations which have had substantial impacts on the survival and quality of life of patients (PhRMA, 2016), as well as on costs for healthcare systems. Although the data we use are only representative of one clinical area, in comparison with the previous empirical investigations of strategic interaction in price / profit regulation at the international level (Egan and Philipson, 2013; Frech et al., 2023), they have the advantage of allowing us to study the price and the size of the market at the product level, rather than relying on price indices at the country level.

Although our theoretical analysis modelled only two countries, the empirical analysis necessarily considers several. This does not pose a problem for our test of the U-shaped relationship between equilibrium prices and market size as described in section 4.5, and an approach which models two countries theoretically and multiple countries empirically reflects similar approaches taken in other studies. For example, Devereux et al. (2008) model two symmetric countries and consider several heterogeneous countries in their empirical analysis, as do Beshkar et al. (2015).

5.1 Data

Data on quarterly prices, reimbursement status, patent status and product launch date for the period 2007–2017 were retrieved from the Pricing Insights IMS Health database for the 25 countries that, in 2007, were members of the OECD. Given our focus on regulated prices, we exclude from the analysis prices in the United States because they are unregulated. Portugal is also omitted, because the Pricing Insights IMS Health database provides only partial coverage for the period of interest. The sample used for the analysis therefore includes 23 OECD countries.

For cross-country comparisons, we follow Kanavos and Vandoros (2011) and express prices in Euro by using period specific exchange rates and we compute the product's price per mg,

[13]Confidential discounts are heavily used in the US (Danzon and Chao, 2000b), which is excluded from the analysis for the reasons explained below, and less so in other countries.

because the same product may be available with a different pack size and/or different strength in different countries. When different pack sizes and/or different strengths are available for the same product at the same time within one country, we refer to the lowest price per mg, assuming that this is the relevant price for the payer.[14]

Table 3 in Appendix B.1 presents a full list of the neoplasm causes that we consider. Country-level disease prevalence data, measured by the number of individuals suffering from a disease in a given year, are used to proxy a product's market size. Data are extracted from the Global Burden of Diseases (GBD) 2015 database (Catalá López and Tabarés Seisdedos, 2016).[15] We considered the therapeutic indication(s) reported by the EMA 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 haematology and one for oncology. When a drug is indicated for more than one disease, prevalence is obtained as the sum over all diseases. Since prevalence data are only available at five year intervals, prevalence is considered constant within the intervening four years. Table 4 in Appendix B.1 lists the drugs included in the final sample,[16] together with the number of countries which adopted them. Our empirical analysis converts the prevalence data into a measure of a drug's relative market size in each country, by dividing the drug's country-level prevalence by the sum of the prevalence levels across all of the countries that we extracted from the IMS Health database, including those of the United States and Portugal.

Data for GDP per capita and the export of medicinal and pharmaceutical products, which are used to proxy the theoretical parameters κ (country-specific willingness to pay) and λ (the fraction of global firm profit accruing to a country), are gathered from the World Bank Indicators and the United Nations Conference on Trade and Development Statistics, respectively. For consistency with the price data, all values are converted into current Euro using the quarterly exchange rate as reported in the Pricing Insights IMS Health database.

[14] Given the characteristics of oncology treatments, for the majority of observations (80.8%) we refer to the *price to the hospital* per mg. However, for countries in which mandatory rebates are in force, we consider the *manufacturer less mandatory rebates price* per mg (14.9% of observations). For the remaining observations, where neither price is available, we refer to the *price to pharmacies* (4%) or to the *retail price* (0.1%).

[15] The GBD cause and sequelae list is organised hierarchically; we consider the prevalence at Level 3, which contains the finest level of detail for causes captured in GBD 2015.

[16] We exclude 25 drugs from the analysis for a range of reasons which are explained in Appendix B.1, leaving 83 for the estimation sample. Some single observations on the 83 included drugs were dropped because they refer to parallel imports, for which prices are not directly controlled by the national regulator.

5.2 Descriptive statistics

Table 1 presents a summary of a normalized measure of the price per mg – the country-level product price divided by the product's average price – together with relative market size, GDP per capita and pharmaceutical export volume, for the countries that are included in the empirical analysis. Only two countries have average relative market sizes exceeding 10%: the United States (not listed in Table 1 because it is not included in the estimation sample), with a relative market size of 35%, is by far the largest; Japan, with 14%, is in second place. The standard deviations for relative market size show that within-country variability is limited because the prevalence of one cancer relative to the others tends to be similar across countries.

Figure 3 shows the relationship between normalised price and the decile of relative market size. The figure is suggestive of the existence of a U-shaped relationship between the two variables, reaching a minimum around the 7th decile.

Figure 4 plots the estimate of the Kernel density of relative market size. The density is unevenly distributed, with a right skew which shows that a small number of observations have a very high relative market size. Since the main goal of our empirical analysis is to study the relationship between prices and relative market size, the accuracy of predictions for ranges of relative market size with very few observations might be poor. For this reason, for our baseline analysis we drop the 1.9% of observations for which the relative market size exceeds 13%, the value at which there is a clear drop in the density. We also carry out our analysis on the full sample, with no trimming.

5.3 Empirical specification

Our baseline analysis uses ordinary least squares to estimate the following empirical specification:

$$\ln[p_{i,c,t}] = \alpha + \sum_{k=1}^{K} \mu_k \left(\frac{N_{i,c,t}}{N_{i,t}} \right)^k + \boldsymbol{\delta}' \mathbf{Z}_{c,t} + \zeta_i + \epsilon_{i,c,t}, \tag{12}$$

where i denotes the drug, c the country and t time. $\ln[p_{i,c,t}]$ is the natural logarithm of the price per mg of drug i in country c at time t. The main variable of interest is $N_{i,c,t}/N_{i,t}$, the relative market size of drug i in country c at time t. $N_{i,c,t}$ is the total prevalence in country c of the diseases that can be treated by product i and $N_{i,t}$ is the sum of the prevalences over all 25 countries, including Portugal and the United States.

The other regressors in Eq. (12) are as follows:

- $\mathbf{Z}_{c,t}$ is a vector of country- and time-varying controls which includes the natural logarithms

	Year first observed	Number of observations	Number of products	Normalised price per mg		Relative market size		GDP per capita (€)		Pharmaceutical exports (€million)	
				Mean	SD	Mean	SD	Mean	SD	Mean	SD
Austria	2007	1364	73	1.0705	0.1128	0.0076	0.0011	38207	2168	3210	7261
Belgium	2007	1070	51	0.9876	0.1134	0.0111	0.0020	35310	1939	13653	3691
Czech Republic	2011	546	46	0.8301	0.2439	0.0091	0.0032	15823	741	569	26
Denmark	2007	1283	71	1.0369	0.1057	0.0058	0.0017	46556	2211	2633	655
Finland	2007	1077	52	1.0308	0.1187	0.0052	0.0012	37437	1735	207	51
France	2007	1186	58	1.0044	0.1898	0.0754	0.0113	32257	1314	6085	1187
Germany	2007	1375	73	0.9727	0.1589	0.0873	0.0138	35392	2798	20809	4244
Greece	2007	668	50	0.9440	0.1284	0.0093	0.0028	18136	1969	36	12
Hungary	2007	626	35	0.9453	0.1187	0.0097	0.0038	10610	725	770	342
Ireland	2007	1085	56	1.2151	0.1524	0.0038	0.0009	45837	8133	8665	2551
Italy	2007	1152	56	1.0017	0.1328	0.0703	0.0114	27240	589	3431	1103
Japan	2011	787	51	1.0875	0.3469	0.1372	0.0430	33129	2961	1204	146
Korea	2011	474	32	0.7192	0.2483	0.0230	0.0149	22200	2928	1124	511
Luxembourg	2010	150	7	0.9161	0.2510	0.0004	0.0001	87106	4598	146	55
Netherlands	2008	613	38	1.0395	0.1092	0.0148	0.0061	39825	1264	9662	3102
Norway	2007	1121	65	0.9777	0.1280	0.0054	0.0015	70315	5248	136	24
Poland	2008	228	16	1.0927	0.4972	0.0178	0.0040	10701	742	275	98
Slovak Republic	2010	481	35	0.8977	0.1145	0.0043	0.0016	14347	664	37	8
Spain	2007	1065	54	0.9755	0.1047	0.0446	0.0067	23197	830	2505	715
Sweden	2007	956	57	1.0190	0.1567	0.0088	0.0032	44263	3618	1770	453
Switzerland	2007	1046	54	1.1620	0.1420	0.0071	0.0027	65026	8138	22744	5636
Turkey	2010	409	26	0.4536	0.1119	0.0222	0.0161	9389	604	187	88
United Kingdom	2007	1393	72	0.9752	0.1815	0.0646	0.0137	34254	3623	7897	2418
Full sample	2007	20155	83	1.0000	0.2052	0.0324	0.0377	36428	15841	5927	7200

Table 1: Summary statistics for the estimation sample.

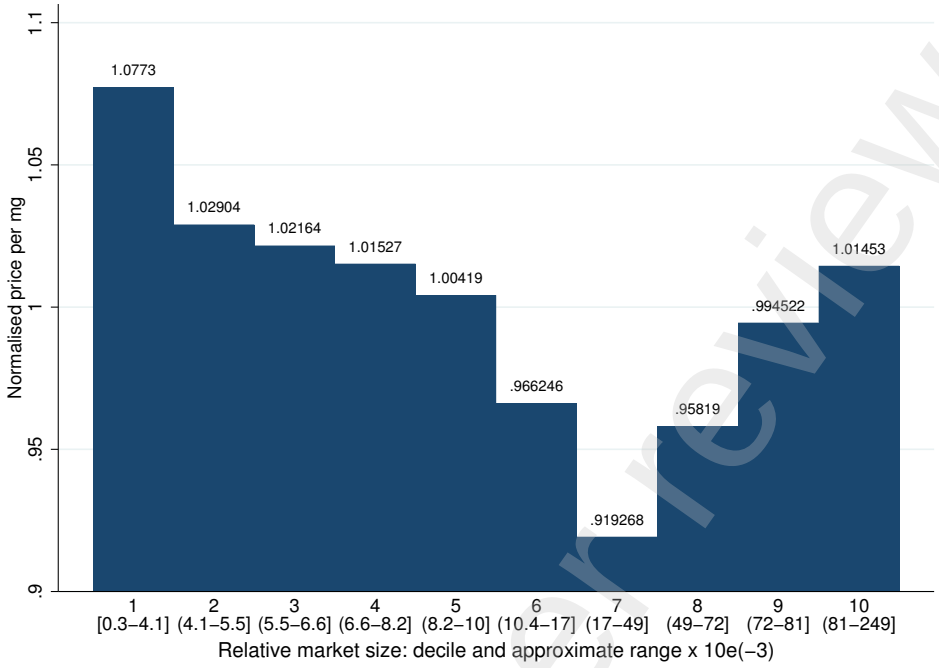


Figure 3: The relationship between normalised price and the decile of relative market size.

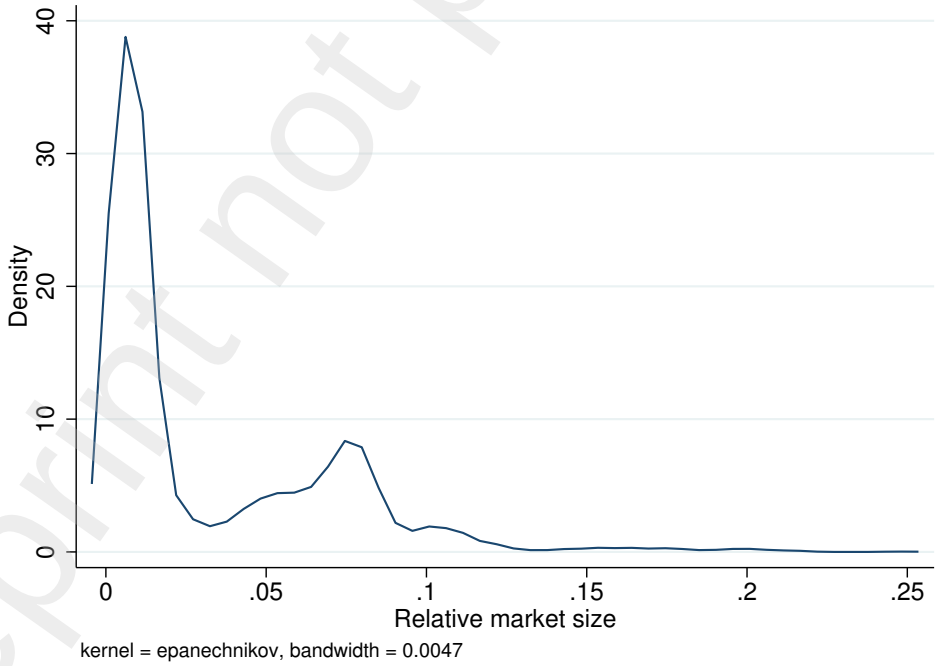


Figure 4: Kernel density estimate for relative market size.

of GDP per capita and pharmaceutical exports. Since the value of pharmaceutical exports largely depends on prices regulated by importing countries, it seems reasonable to assume that the explanatory variable is exogenous.

- ζ_i is a product fixed effect that is intended to capture the drug i's quality and therapeutic advance, both of which are unobserved. This variable allows us to control for the intrinsic characteristics of drugs, which can be a primary driver of prices, and is included because our dependent variable is the price per mg, but the standard course of treatment varies across drugs.

We also considered including country-level fixed effects in Eq. (12), to control for time-invariant, cross-country, heterogeneity. Although this might be reasonable in principle, it is problematic given our focus on the role of relative market size. As already noted in section 5.2, the variability of our measure of relative market size tends to be very limited across products. This means that, to a large extent, including country fixed effects prevents us from investigating the role of relative market size.

We investigate the sensitivity of results to the inclusion of a variable which measures the number of years between t and the launch date of a product (in the first country of launch). This variable is intended to be a proxy for the degree of obsolescence of a product. It may be an important explanatory variable, given that we have more than one observation per product over time and evidence suggests that prices tend to fall over time (Cabrales and Jiménez-Martín, 2013; Kanavos and Vandoros, 2011; Danzon and Chao, 2000a) owing to, for example, anticipation of increased competition following patent expiry and the launch of a new product which treats the same indication.

We investigate a potentially non-linear relationship between price and relative market size by using the log of price as the dependent variable and specifying a polynomial of degree K for relative market size. We consider two approaches to specifying the functional form for relative market size: 1. a quadratic function ($K = 2$); 2. a semi-parametric approach to choosing the optimal degree of polynomial, which is selected according to a cross-validation criterion.[17]

The above specifications constitute the main tests of our theoretical predictions. We check the robustness of our results considering parametric and non-parametric estimation methods, including GLM, cubic spline and a fully non-parametric estimation procedure, the Kernel-based regularized Least Squares.

[17]This splits the sample into a training and a validating set, with the training set being used to estimate the parameters and the best model selected according to its predictive performance in the validating set (Stone, 1974; Geisser, 1975; Zhang and Yang, 2015).

5.4 Results

	Dependent variable: ln(price per mg)			
	(1)	(2)	(3)	(4)
Relative market size	-3.325***	-3.817***	-7.099***	-7.031***
	(1.106)	(1.166)	(2.531)	(2.509)
Relative market size (squared)	30.050**	33.686***	115.043**	106.110**
	(12.162)	(12.733)	(52.924)	(52.046)
Relative market size (cubed)			-495.295	-422.165
			(306.631)	(303.271)
Natural logarithm of GDP per capita	0.156***	0.147***	0.147***	0.140***
	(0.019)	(0.019)	(0.018)	(0.018)
Natural logarithm of pharmaceutical exports	0.020***	0.023***	0.021***	0.024***
	(0.002)	(0.002)	(0.002)	(0.002)
Number of years since launch date		-0.024***		-0.024***
		(0.004)		(0.004)
Number of observations	19766	19766	19766	19766
U-shape test (*p-value*)	0.017	0.013		
Extreme point	0.055	0.057		

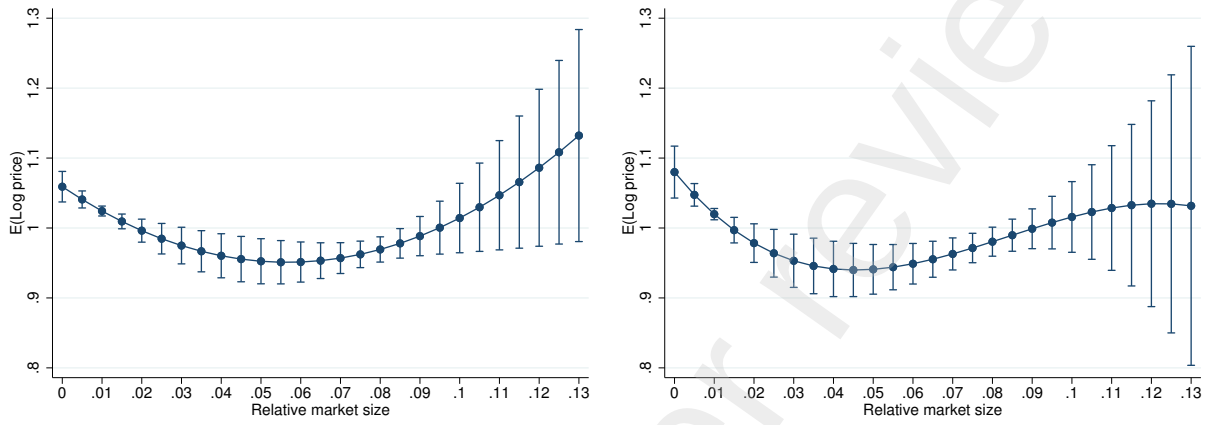
Models include product-level fixed effects.
Standard errors (in parentheses) are clustered at the product level.
* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 2: Results of the main empirical analysis.

Table 2 reports the results of our baseline analysis. Column (1) refers to the estimation of Eq. (12) using a quadratic polynomial for relative market size. Coefficients for the relative market size variable and its square are statistically significant at the 1% and 5% levels, respectively, and the signs of their coefficients are consistent with the idea of a U-shaped relationship existing between price and relative market size. A formal test of a U-shaped relationship, that of Lind and Mehlum (2010), confirms this ($p \approx 0.017$) and suggests that price reaches its minimum value when relative market size is equal to 5.5%.[18] In line with our theoretical predictions, the coefficients of GDP per capita and pharmaceutical exports, our proxies for the parameters κ and λ, are both positive and significant at the 1% level. Column (2) of Table 2 shows that the coefficient on the number of years since launch variable is statistically significant and suggests

[18] Lind and Mehlum (2010) show that the widespread approach to testing for a U- (or hump-) shape based on the statistical significance and signs of the linear and the quadratic term is flawed. In particular, they show that statistical significance of the linear term is not a necessary condition, whereas significance of the quadratic term is necessary but not sufficient when the data range is a subset of $\mathbb{R}$. The test of Lind and Mehlum (2010) tests the null hypothesis that the relationship is monotone or inverse U-shaped against the alternative hypothesis of a monotone decreasing relationship at low values and a monotone increasing relationship at high values of the variable of interest.

that prices fall by an estimated 2.4% per year. For this reason, we include this variable in all subsequent analysis. Its inclusion has little impact on the other estimates. In particular, results continue to suggest a U-shaped relationship between relative market size and price ($p \approx 0.013$), and there is little change in the estimated extreme point.



(a) Second-degree polynomial. **(b)** Third-degree polynomial.

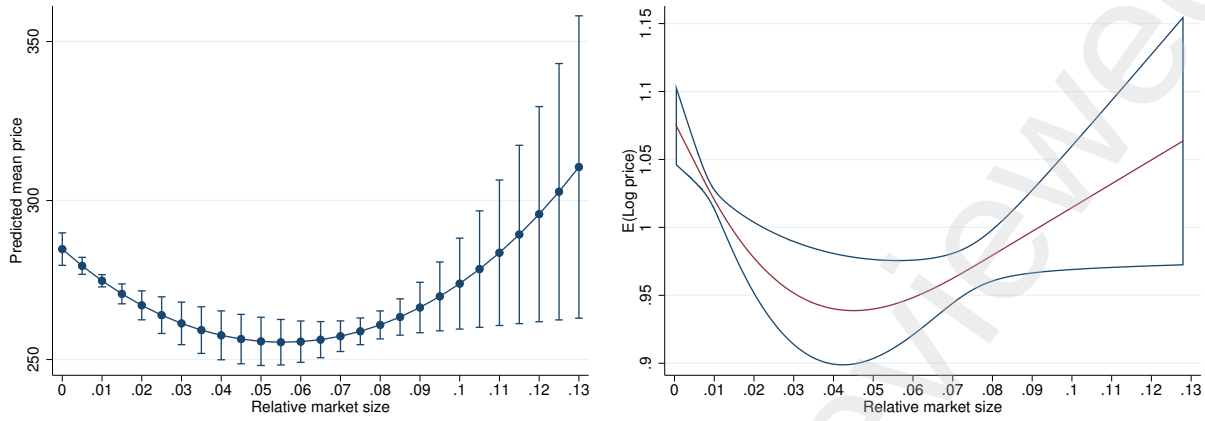
Figure 5: The relationship between price and relative market size for the models presented in columns (2) and (4) of Table 2. Predictive margins with 95% CI.

The cross validation criterion approach to selecting the optimal degree of polynomial for relative market size suggests that a polynomial of degree three should be used, and columns (3) and (4) of Table 2 present the results for these models.[19] It is not possible to apply the U-shape test to the models in columns (3) and (4) because relative market size is not specified as a quadratic function. Nevertheless, the coefficients of the polynomial continue to suggest a U-shaped relationship, as the subsequent graphical analysis shows. The results in columns (3) and (4) also show that the third degree polynomial specification has little impact on the estimated coefficients for the control variables.

Figure 5 shows the predicted relationships between the natural logarithm of price and relative market size for the results presented in columns (2) and (4) of Table 2.[20] The shape of the two figures is similar up to a relative market size of about 0.11, and the minimum points for the two figures are also similar (a minimum of 0.951 for a relative market size of 5.7% in the left figure and a minimum of 0.940 for a relative market size of 4.5% in the right figure). Allowing for

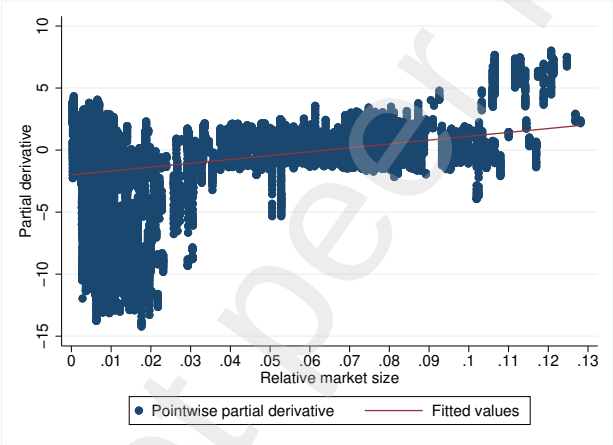
[19] Three is the optimal degree of the polynomial for our preferred model, which includes the time since first launch, and we also adopt it for the regression whose results are reported in column (3) of Table 2, even though the optimal degree for this case is five.

[20] Note that the large size of confidence intervals for comparatively large relative market sizes is consistent with the density plot in Figure 4.



(a) GLM, 2nd degree polynomial. Predictive margins with 95% CI.

(b) Cubic spline. Predictive margins with 95% CI.



(c) KRLS

Figure 6: The relationship between price and relative market size using three alternative models.

greater flexibility in the functional form leads to a flatter curve above a relative market size of approximately 0.11 for the case of a polynomial of degree three.

Figure 6 shows graphically the results concerning the relationship between relative market size and price for three alternative models that we use as robustness checks. The first (Figure 6a) is an alternative parametric approach, and in particular a Generalized linear Model (GLM) with a polynomial of degree 2, log as link function and the Gamma distribution for errors (as suggested by the modified Park test (Manning and Mullahy, 2001)). Figure 6b shows the results for a cubic spline with 3 knots, located at the default percentiles of relative market size suggested by Harrell et al. (2001) (10^{th}, 50^{th} and 90^{th}). Finally, we adopt a fully non-parametric approach, Kernel-Based Regularized Least Squares (KRLS). KRLS is a machine learning method (Hainmueller

and Hazlett, 2014) that has at least two interesting properties for our setting. First, unlike other methods used so far, it does not require any assumptions concerning specific functional forms. Second, it allows for interactions among virtually all of the parameters, which may be interesting, given the complexity of the relationships shown by the theory. This procedure provides an estimate of the derivative of price with respect to the variable of interest, relative market size, for each data point. Figure 6c shows that the derivatives tend to be lower, and negative on average, for low values of the relative market size and positive for high values, which is again consistent with the idea of a U-shape relationship between market size and price.

The results of the analysis conducted on the untrimmed sample are in line with those presented here for the trimmed sample (see, Appendix B.2). Overall, our empirical results are consistent with our theoretical predictions of a U-shaped relationship existing between equilibrium price and relative market size, as described at the end of Section 4.5.

5.5 Policy implications

The relative market size of a procurement authority may be seen, at least to some extent, as a policy decision, as witnessed by the debate on the possibility of adopting joint procurement, with the idea that a larger procurement authority always achieves lower prices (Vogler et al., 2018; Larsen et al., 2021). Our results show that this is not necessarily true once the implications for R&D incentives and the resulting strategic position of the authority are taken into account.

The quantitative estimates presented above allow us to explore, at least tentatively, which countries are more likely to achieve price reductions through joint procurement, assuming the aim is the minimization of pharmaceutical prices. The estimated extreme point for our preferred model (Table 2, column (4)) corresponds to a relative market size of 4.5%. In our data, there are only five countries whose average relative market size exceeds this threshold: Japan, Germany, France, Italy and the UK. For these countries, the expected impact of an expansion of their relative market size is an increase in prices. On the other hand, particularly small countries may have an interest in joining their procurement. In this sense, it is not surprising that the most comprehensive agreement for joint pharmaceutical procurement that is currently in operation is the Beneluxa intiative, which involves (following the entry order) Belgium, the Netherlands, Luxembourg, Austria and Ireland. The average relative market size for these countries in our data is, respectively, 1.11%, 1.48%, 0.04%, 0.76% and 0.38%. Hence, all of them are well below the 4.5% threshold. By summing up the average values of the relative market sizes for these countries, we can obtain a proxy for the relevant relative market size of the "joint authority", which is 3.77%, still well below the threshold. According to the estimates based on our data, other

things being equal, the predicted reductions in prices achieved through the Beneluxa intiative range from 5.3% for the Netherlands to 12.5% for Luxembourg.

These results should be interpreted cautiously. One caveat is that our data do not cover the whole global market. Moreover, a change in the relative market size of a number of countries might shift, to some extent, the position of the extreme point. Nonetheless, there are two messages that we believe should be seriously considered. The first is that very small countries have the largest potential to reduce prices through joint procurement. The second is that, if the relevant market for the new procurement authority is too large, prices may increase, at least for those countries whose initial market size is comparatively large.

6 Conclusion

With a large share of pharmaceutical R&D being undertaken by the private sector, patents are one of the main tools deployed to enhance dynamic efficiency. However, the related monopolistic profits are crucially affected by regulators' price setting decisions, which also need to take static efficiency into account. A regulator who raises prices in one country may bring benefits to other countries too, by fostering innovation whose results typically become available on a global scale. To the best of our knowledge, this is the first study investigating the mechanisms underlying strategic interaction in price setting related to R&D incentives at the international level.

Our model of strategic interaction among countries in pharmaceutical price regulation shows that if the weight of consumer surplus in the regulator's objective function is sufficiently large, relative to that of the industry profit, prices are strategic substitutes. Under these circumstances, free-riding in pharmaceutical price regulation can arise. We characterise two types of Nash equilibrium. In one, a country can exploit its strategic position to set the price at the minimum level the firm is willing to accept in order to serve the domestic market, whereas the other country responds optimally with a price above the reservation price. *Ceteris paribus*, small countries are more likely to price at the reservation price. Conditional on this being the relevant equilibrium price, an increase in the relative market size of the small country reduces prices, because the opportunity cost for the firm of not serving a market is increasing in its size. The second type of equilibrium becomes relevant if the relative size of both markets is sufficiently large. Conditional on this being the relevant equilibrium, an increase in the relative market size of one country increases its equilibrium price. Intuitively, this is due to the fact that the same price increase will be a more powerful incentive to increase R&D investment if implemented in a country whose market is large, because it leads to a large increase in profits.

The combination of these two equilibria leads to the prediction of a U-shaped relationship between price and relative market size. We find empirical support for this hypothesis using data on prices of 83 cancer drugs in 23 OECD countries. The results of our analysis allow us to reconcile two contrasting predictions concerning the relationship between drug prices and market size: the idea that the monopsony power of regulators grows with a larger market, thus allowing them to obtain lower prices; the theoretical result that, in an interior equilibrium, prices are higher where markets are larger, because the size of the spillover effect of a price increase in terms of R&D incentive is greater.

One implication of our results is that small countries are more likely than large countries to obtain reductions in prices through joint procurement initiatives. According to our tentative estimates, the most comprehensive existing initiative, in terms of products covered, the Beneluxa, has the characteristics to allow each of the participating countries to lower their prices. However, initiatives leading to the creation of procurement authorities with very large relative market sizes are less likely to achieve this objective for all participating countries, other things being equal, due to the less favourable strategic position of a regulator with very large market size. In general, the country-specific sign of the impact of moving from national to joint procurement authorities depends on the relative size of both the original and the final market.

Although we believe that the model can make a valuable contribution to the literature by providing a basis for a formal analysis of strategic interaction in the trade-off between static and dynamic efficiency, we also acknowledge some limitations that future research should aim to overcome. For instance, an extension of the theoretical model to allow pricing decisions to be sequential and/or repeated, as they tend to be for the decisions considered in our empirical analysis, would be valuable. It should also be noted that our data only allow for an analysis of pricing policies conditional on adoption. It is hoped that the availability of longer time series will allow future research to exploit the information related to a country's decision concerning whether or not to adopt a new drug. Finally, it would be interesting to investigate whether the empirical results we find for a large set of cancer drugs are confirmed by analyses based on more comprehensive datasets, including medicines from several therapeutic classes.

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Conflict of interest

The authors declare they have no conflict of interest.

References

Barfield, C. E. and Groombridge, M. A. (1998). The economic case for copyright owner control over parallel imports. *The Journal of World Intellectual Property*, 1(6):903–939.

Barfield, C. E. and Groombridge, M. A. (1999). Parallel trade in the pharmaceutical industry: implications for innovation, consumer welfare, and health policy. *Fordham Intell. Prop. Media & Ent. LJ*, 10:185.

Barton, J. H. and Emanuel, E. J. (2005). The patents-based pharmaceutical development process: Rationale, problems, and potential reforms. *Journal of the American Medical Association*, 294(16):2075–2082.

Benda, M.-C., Mallory, C., and Lu, H. (2004). An econometric estimation of pricing of brand-name drugs. *Applied Health Economics and Health Policy*, 3(1 suppl):S12.

Bennato, A. R. and Valletti, T. (2014). Pharmaceutical innovation and parallel trade. *International Journal of Industrial Organization*, 33:83–92.

Beshkar, M., Bond, E. W., and Rho, Y. (2015). Tariff binding and overhang: theory and evidence. *Journal of International Economics*, 97(1):1–13.

Brekke, K. R., Holmås, T. H., and Straume, O. R. (2015). Price regulation and parallel imports of pharmaceuticals. *Journal of Public Economics*, 129:92–105.

Cabrales, A. and Jiménez-Martín, S. (2013). The determinants of pricing in pharmaceuticals: are US prices really so high? *Health Economics*, 22(11):1377–1397.

Catalá López, F. and Tabarés Seisdedos, R. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*, 8(388):1545–1602.

Chown, J., Dranove, D., Garthwaite, C., and Keener, J. (2019). The opportunities and limitations of monopsony power in healthcare: evidence from the United States and Canada. Technical report, National Bureau of Economic Research.

Daalen, J. M. J., den Ambtman, A., Van Houdenhoven, M., and van den Bemt, B. J. (2021). Determinants of drug prices: a systematic review of comparison studies. *BMJ Open*, 11(7):e046917.

Danzon, P. M. (1998). The economics of parallel trade. *Pharmacoeconomics*, 13(3):293–304.

Danzon, P. M. and Chao, L.-W. (2000a). Cross-national price differences for pharmaceuticals: how large, and why? *Journal of Health Economics*, 19(2):159–195.

Danzon, P. M. and Chao, L.-W. (2000b). Does regulation drive out competition in pharmaceutical markets? *The Journal of Law and Economics*, 43(2):311–358.

Danzon, P. M. and Towse, A. (2003). Differential pricing for pharmaceuticals: reconciling access, R&D and patents. *International Journal of Health Care Finance and Economics*, 3(3):183–205.

Devereux, M. P., Lockwood, B., and Redoano, M. (2008). Do countries compete over corporate tax rates? *Journal of Public Economics*, 92(5):1210–1235.

Dixit, A. (1986). Comparative statics for oligopoly. *International Economic Review*, 27:107–122.

Dubois, P., Lefouili, Y., and Straub, S. (2021). Pooled procurement of drugs in low and middle income countries. *European Economic Review*, 132:103655.

Egan, M. and Philipson, T. J. (2013). International health economics. NBER Working Paper Series. Working Paper No. 19280.

Ekelund, M. and Persson, B. (2003). Pharmaceutical pricing in a regulated market. *Review of Economics and Statistics*, 85(2):298–306.

Espin, J., Rovira, J., and Olry de Labry, A. (2011). Working paper 1: external reference pricing. *World Health Organisation and Health Action International*.

Espin, J., Rovirai, J., Ewen, M., and Laing, R. (2014). Mapping external reference pricing practices for medicines. Working papers, Health Action International and the Andalusian School of Public Health.

EvaluatePharma (2021). *World Preview 2021, Outlook to 2026*. EvaluatePharma.

Finus, M. (2001). *Game Theory and International Environmental Cooperation*. Edward Elgar, Cheltenham, UK; Northampton, MA, USA.

Frech, H., Pauly, M. V., Comanor, W. S., Martinez, J. R., et al. (2023). Pharmaceutical Pricing and R&D as a Global Public Good. Technical report, National Bureau of Economic Research.

Geisser, S. (1975). The predictive sample reuse method with applications. *Journal of the American Statistical Association*, 70(350):320–328.

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

Grossman, G. M. and Lai, E. L. (2004). International protection of intellectual property. *The American Economic Review*, 94(5):1635–1653.

Grossman, G. M. and Lai, E. L.-C. (2008). Parallel imports and price controls. *The RAND Journal of Economics*, 39(2):378–402.

Harrell, F. E. et al. (2001). *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*, volume 608. Springer.

Helble, M. and Aizawa, T. (2017). International trade and determinants of price differentials of insulin medicine. *Health Policy and Planning*, 32(1):1–10.

Hogerzeil, H. V. and Mirza, Z. (2011). The World Medicines Situation 2011: Access to Essential Medicines as Part of the Right to Health. *Geneva: World Health Organization*.

Hooper, C. A. and Henderson, D. (2022). Expensive prescription drugs are a bargain. *Wall Street Journal*.

Kanavos, P. G. and Vandoros, S. (2011). Determinants of branded prescription medicine prices in OECD countries. *Health Economics, Policy and Law*, 6(03):337–367.

Kyle, M. and Qian, Y. (2014). Intellectual property rights and access to innovation: evidence from TRIPS. NBER Working Paper No. 20799.

Kyle, M. K. (2022). Incentives for pharmaceutical innovation: What's working, what's lacking. *International Journal of Industrial Organization*, 84:102850.

Kyle, M. K., Ridley, D. B., and Zhang, S. (2017). Strategic interaction among governments in the provision of a global public good. *Journal of Public Economics*, 156:185–199.

Lakdawalla, D. and Yin, W. (2015). Insurers' negotiating leverage and the external effects of Medicare part D. *Review of Economics and Statistics*, 97(2):314–331.

Larsen, B.-I., Kluge, H., Muscat, N. A., Hågå, A., Sanne, A.-P., Garner, S., Ravnestad, S. E., Harris, R., Aarsand, R., Kniazkov, S., et al. (2021). The Oslo Medicines Initiative: improving access to high-cost medicines in Europe. *Eurohealth*, 27(32):36.

Li, C. and Maskus, K. E. (2006). The impact of parallel imports on investments in cost-reducing research and development. *Journal of International Economics*, 68(2):443–455.

Lind, J. T. and Mehlum, H. (2010). With or without U? the appropriate test for a u-shaped relationship. *Oxford Bulletin of Economics and Statistics*, 72(1):109–118.

Lu, Z. J. and Comanor, W. S. (1998). Strategic pricing of new pharmaceuticals. *Review of Economics and Statistics*, 80(1):108–118.

Manning, W. G. and Mullahy, J. (2001). Estimating log models: to transform or not to transform? *Journal of Health Economics*, 20(4):461–494.

Mulcahy, A. W., Whaley, C. M., Tebeka, M. G., Schwam, D., Edenfield, N., and Ornelas, A. U. B. (2021). *International prescription drug price comparisons: current empirical estimates and comparisons with previous studies*. RAND.

Murdoch, J. C. and Sandler, T. (1997). Voluntary cutbacks and pretreaty behavior: The Helsinki protocol and sulfur emissions. *Public Finance Review*, 25(2):139–162.

Newhouse, J. P. (2004). How much should Medicare pay for drugs? *Health Affairs*, 23(1):89–102.

OECD (2008). Pharmaceutical pricing policies in a global market. Technical report. OECD Publishing.

OECD (2018). *Pharmaceutical Innovation and Access to Medicines*.

PhRMA (2016). *A Decade of Innovation in Cancer: 2006-2016*. PhRMA.

Puig-Junoy, J. and González López-Valcárcel, B. (2014). Launch prices for new pharmaceuticals in the heavily regulated and subsidized Spanish market, 1995–2007. *Health Policy*, 116(2):170–181.

Reisinger, M., Saurí, L., and Zenger, H. (2019). Parallel imports, price controls, and innovation. *Journal of Health Economics*, 66:163–179.

Stone, M. (1974). Cross-validatory choice and assessment of statistical predictions. *Journal of the Royal Statistical Society: Series B (Methodological)*, 36(2):111–133.

Vogler, S., Paris, V., and Panteli, D. (2018). *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* World Health Organization, Regional Office for Europe.

Von der Schulenburg, F., Vandoros, S., and Kanavos, P. (2011). The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors. *Health Economics Review*, 1(1):18.

Wagner, J. L. and McCarthy, E. (2004). International differences in drug prices. *Annual Review of Public Health*, 25:475–495.

WHO (2015a). Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Technical report, WHO, European Regional Office.

WHO (2015b). *WHO Guideline on Country Pharmaceutical Pricing Policies*. World Health Organization.

Zhang, Y. and Yang, Y. (2015). Cross-validation for selecting a model selection procedure. *Journal of Econometrics*, 187(1):95–112.

Zodrow, G. R. and Mieszkowski, P. (1986). Pigou, Tiebout, property taxation, and the underprovision of local public goods. *Journal of Urban Economics*, 19(3):356–370.

A Appendices: theoretical analysis

A.1 Relationship between reservation prices and relative market size

Consider the system of equations defining the reservation prices r^A and r^B as a function of the relative market sizes in countries A and B:

$$\begin{aligned}\Pi^A(r^A(n^A), r^B(n^A), n^A) &= n^A(r^A - m)\hat{q}^A - C^A = 0,\\ \Pi^B(r^A(n^A), r^B(n^A), n^A) &= (1-n^A)(r^B - m)\hat{q}^B - C^B = 0.\end{aligned} \tag{13}$$

Expressions for the partial derivatives of r^A and r^B with respect to n^A may be obtained by differentiating Eq. (13) with respect to n^A and applying Cramer's rule. For example, for the case of r^A:

$$\frac{\partial r^A}{\partial n^A} = \frac{\begin{vmatrix} -\Pi^A_{n^A} & \Pi^A_{r^B} \\ -\Pi^B_{n^A} & \Pi^B_{r^B} \end{vmatrix}}{|\mathbf{K}|}, \tag{14}$$

where $|\mathbf{K}| = \Pi^A_{r^A}\Pi^B_{r^B} - \Pi^A_{r^B}\Pi^B_{r^A}$ is strictly positive when the product of the direct effects of an increase in reservation price on own-country profits exceeds the indirect effects. The numerator of the RHS of Eq. (14) may be written as:

$$\begin{aligned}-\Pi^A_{n^A}\cdot\Pi^B_{r^B} + \Pi^B_{n^A}\cdot\Pi^A_{r^B} = &-(r^A - m)\left[\hat{q}^A + n^A\frac{\partial \hat{q}^A}{\partial n^A}\right]\cdot(1-n^A)\left[\hat{q}^B + (r^B-m)\frac{\partial \hat{q}^B}{\partial r^B}\right] + \\ &+(r^B-m)\left[-\hat{q}^B + (1-n^A)\frac{\partial \hat{q}^B}{\partial n^A}\right]\cdot n^A(r^A-m)\frac{\partial \hat{q}^A}{\partial r^B}.\end{aligned} \tag{15}$$

The final term on the RHS of Eq. (15), $\partial\hat{q}^A/\partial r^B$, is strictly positive because an increase in r^B increases $\hat{q}^A$ via its impact on I^*. The analysis in section 4.2 shows that $\partial\hat{q}^B/\partial r^B$ is strictly positive providing the reservation price is smaller than the price optimally set by the regulator. Hence, other things being equal, own country profits increasing in own country relative market size ($\Pi^A_{n^A} > 0$, and therefore $\Pi^B_{n^A} < 0$) is a sufficient condition for $\partial r^A/\partial n^A < 0$. Eq. (15) also shows that, with n^A sufficiently small, the term in the first row is unambiguously negative, with the other term going to zero as n^A goes to zero. Hence $\partial r^A/\partial n^A < 0$.

A.2 Implications of the assumptions on $\hat{q}^A(\cdot)$

In section 4.2 we introduce the assumption that $\hat{q}^A(\cdot)$ is strictly concave in p^A. Here we investigate the conditions under which it holds and show that these are satisfied for some very standard functional forms for the production function δ.

Given the definition of $\hat{q}^A$ in Eq. (7),

$$\frac{\partial^2\hat{q}^A}{\partial p^A\partial p^A} = \frac{\kappa^A}{b^A}\left[\frac{\partial^2\delta}{\partial I^2}\left(\frac{\partial I^*}{\partial p^A}\right)^2 + \frac{\partial\delta}{\partial I}\frac{\partial^2 I^*}{\partial p^A\partial p^A}\right]. \tag{16}$$

The application of the implicit function theorem to Eq. (5) enables us to obtain an expression for $\partial I^*/\partial p^A$, from which the expression for $\partial^2 I^*/\partial p^A\partial p^A$ follows. After substituting these partial and cross-partial

derivatives into Eq. (16) and performing standard algebraic simplifications, Eq. (16) may be written as,

$$\frac{\partial^2 \hat{q}^A}{\partial p^A \partial p^A} = \frac{b^A (b^B)^4 (n^A)^2 (\kappa^A)^3}{\xi^4 (\partial^2 \delta / \partial I^2)} \Big[3 - b^A b^B \frac{\partial^3 \delta / \partial I^3}{\xi (\partial^2 \delta / \partial I^2)^2} \Big], \tag{17}$$

where $\xi = n^A (p^A - m) \kappa^A b^B + (1 - n^A)(p^B - m) \kappa^B b^A > 0$. Since the term that multiplies the expression in brackets is negative, the condition that ensures that $\hat{q}^A$ is strictly concave in p^A is:

$$\frac{\partial^3 \delta / \partial I^3}{(\partial^2 \delta / \partial I^2)^2} < \frac{3\xi}{b^A b^B}. \tag{18}$$

Although the interpretation of the condition is not immediately intuitive, it is easy to see that it holds, for example, for a logarithmic functional form. To see this, start by calculating the ratio between the third derivative and the squared second derivative for the specific functional form of interest. Substitute the value of I^* that solves Eq. (5) into this expression, observing that the first order condition for I^* can be written as $\frac{\partial \delta}{\partial I} = \frac{b^A b^B}{\xi}$. For the case of the logarithmic function, $\frac{\partial^3 \delta / \partial I^3}{(\partial^2 \delta / \partial I^2)^2} = \frac{2\xi}{b^A b^B}$, so that the condition is always satisfied.

A.3 Proof of Proposition 2

When $\alpha^A = 1$, $\partial \hat{q}^A / \partial p^A = 0$ at the value of p^A that maximises W^A. Hence, the sign of $\partial p^{A*} / \partial n^A$ is the same as the sign of $\partial^2 \hat{q}^A / \partial p^A \partial n^A$ (refer to Eq. (10)). This proves the proposition.

In what follows we explore under which conditions $\partial^2 \hat{q}^A / \partial p^A \partial n^A > 0$ is satisfied. From Eq. (7) it may be shown that:

$$\frac{\partial^2 \hat{q}^A}{\partial p^A \partial n^A} = \frac{\kappa^A}{b^A} \left[\frac{\partial^2 \delta}{\partial I^2} \frac{\partial I^*}{\partial p^A} \frac{\partial I^*}{\partial n^A} + \frac{\partial \delta}{\partial I} \frac{\partial^2 I^*}{\partial n^A \partial p^A} \right]. \tag{19}$$

Using a similar approach to that of section A.2, $\partial I^* / \partial n^A$ and $\partial^2 I^* / \partial n^A \partial p^A$ can be derived from Eq. (5). The substitution of these expressions into Eq. (19) leads, after a series of algebraic steps, to the following expression:

$$\begin{aligned} \frac{\partial^2 \hat{q}^A}{\partial p^A \partial n^A} = & \frac{(\kappa^A)^2 b^A (b^B)^3}{\xi^4 (\partial^2 \delta / \partial I^2)} \Big[2 n^A \left[\kappa^A b^B (p^A - m) - \kappa^B b^A (p^B - m) \right] - (p^B - m) \kappa^B b^A + \\ & - \frac{b^A b^B n^A \left[\kappa^A b^B (p^A - m) - \kappa^B b^A (p^B - m) \right]}{\xi} \frac{\partial^3 \delta / \partial I^3}{(\partial^2 \delta / \partial I^2)^2} \Big], \end{aligned}$$

where the definition of ξ is the one introduced in section A.2. Given that $\partial^2 \delta / \partial I^2 < 0$, if:

$$\frac{\partial^3 \delta / \partial I^3}{(\partial^2 \delta / \partial I^2)^2} \left[\kappa^A b^B (p^A - m) - \kappa^B b^A (p^B - m) \right] > \frac{2\xi \left[\kappa^A b^B (p^A - m) - \kappa^B b^A (p^B - m) \right]}{b^A b^B} - \frac{\xi \kappa^B (p^B - m)}{n^A b^B},$$

then $\partial^2 \hat{q}^A / \partial p^A \partial n^A > 0$ and $p^{A*}(p^B)$ is strictly increasing in n^A.

Following the same steps that were described in Appendix A.2, it can be verified that the condition is satisfied for the increasing and concave functional forms most commonly used in economics.

A.4 Proof of Proposition 3

Using similar reasoning to that used in the proof of Proposition 2, when $\alpha^A = 1$, the sign of $\partial p^{A*}/\partial \kappa^A$ is the same as the sign of

$$\frac{\partial^2 \hat{q}^A}{\partial p^A \partial \kappa^A} = \frac{1}{b^A}\left[\frac{\partial \delta}{\partial I}\frac{\partial I^*}{\partial p^A} + \kappa^A\left(\frac{\partial^2 \delta}{\partial I^2}\frac{\partial I^*}{\partial \kappa^A}\frac{\partial I^*}{\partial p^A} + \frac{\partial \delta}{\partial I}\frac{\partial^2 I^*}{\partial \kappa^A \partial p^A}\right)\right]. \tag{20}$$

Expressions for the partial and cross-partial derivatives in this equation can be obtained from Eq. (5) and substituted into Eq. (20), which leads to the following expression:

$$\frac{\partial^2 \hat{q}^A}{\partial p^A \partial \kappa^A} = \frac{(b^A)^2 (b^B)^3 \kappa^A n^A}{\xi^4 (\partial^2 \delta/\partial I^2)}\Big[-2(1-n^A)(p^B - m)\kappa^B - \frac{(b^B)^2 n^A \kappa^A (p^A - m)\partial^3 \delta/\partial I^3}{\xi(\partial^2 \delta/\partial I^2)^2}\Big]. \tag{21}$$

Since the term multiplying the expression in brackets is negative, the assumption $\partial^3 \delta/\partial I^3 \geq 0$ is sufficient for $p^{A*}(p^B)$ to be strictly increasing in κ^A.

A.5 Comparative statics and proof of Proposition 4

For a parameter θ, substitute $p^{A*}(\theta)$ and $p^{B*}(\theta)$ into the first order conditions for welfare maximization:

$$W^A_{p^A}(p^{A*}(\theta), p^{B*}(\theta), \theta) \equiv 0, \tag{22a}$$
$$W^B_{p^B}(p^{A*}(\theta), p^{B*}(\theta), \theta) \equiv 0. \tag{22b}$$

Using a similar approach to that used to derive the comparative statics of reservation prices, differentiating with respect to θ and applying Cramer's Rule leads to the following result for the partial derivative of p^{A*} with respect to θ:

$$\begin{bmatrix} W^A_{p^A p^A} & W^A_{p^A p^B} \\ W^B_{p^B p^A} & W^B_{p^B p^B} \end{bmatrix} \begin{bmatrix} p^{A*}_\theta \\ p^{B*}_\theta \end{bmatrix} = \begin{bmatrix} -W^A_{p^A \theta} \\ -W^B_{p^B \theta} \end{bmatrix}, \tag{23}$$

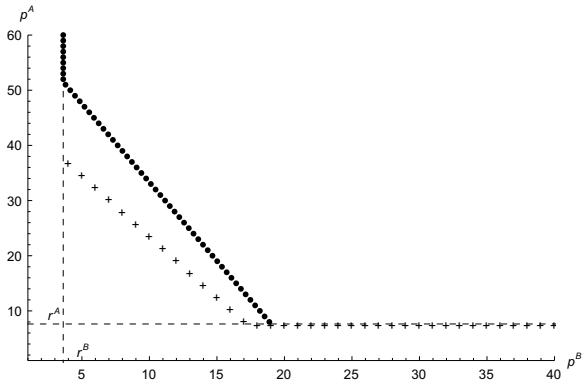
so that:

$$\frac{\partial p^{A*}}{\partial \theta} = \left[-W^A_{p^A \theta} W^B_{p^B p^B} + W^B_{p^B \theta} W^A_{p^A p^B}\right][|\mathbf{H}|]^{-1}, \tag{24}$$

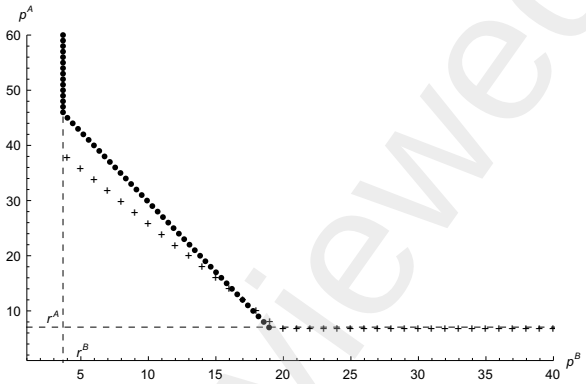
where $\mathbf{H}$ is the determinant of the Hessian of a dynamical system in (p^A, p^B). Given our focus on stationary equilibria, we may refer to the ideas of Dixit (1986) to conclude that $|\mathbf{H}| > 0$. Hence $\text{sign}[\partial p^{A*}/\partial \theta] = \text{sign}\left[-W^A_{p^A \theta} W^B_{p^B p^B} + W^B_{p^B \theta} W^A_{p^A p^B}\right]$. The result may be proved by replacing θ with n^A in Eq. (24). The condition is sufficient because, under the conditions of Proposition 4, the determinant is the sum of two strictly positive terms.

A.6 Simulation

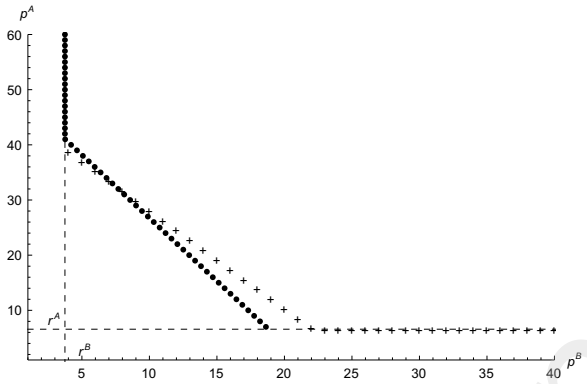
The aim of this section is to use a simulation to illustrate the mechanism described by Corollary 1, which plays an important role for the interpretation of our empirical results. In particular, we show a situation where, as a result of the increase in n^A, country A moves from a corner to an interior solution. We use a logarithmic function for δ, i.e. $\delta(I) = \ln[I]$. The other parameter values are: $\kappa^A = 25$, $\kappa^B = 20$,



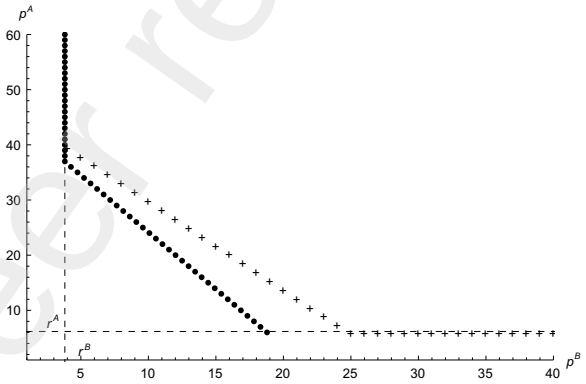
(a) $n^A = 0.22$. Equilibrium prices: $p^A = r^A = 6.17$, $p^B = 19.18$.



(b) $n^A = 0.24$. Equilibrium prices: $p^A = 14.33$, $p^B = 16$.



(c) $n^A = 0.26$. Equilibrium prices: $p^A = 33.58$, $p^B = 7$.



(d) $n^A = 0.28$. Equilibrium prices: $p^A = 41.60$, $p^B = r^B = 3.81$.

Figure 7: Nash equilibria for different values of n^A. '+': $p^{A*}(p^B)$; '•': $p^{B*}(p^A)$. Dashed line represent reservation prices.

$N = 100$, $m = 1$, $\alpha^A = 0.6$, $\alpha^B = 0.8$, $\lambda = 0.85$, $C^A = 25,000$, $C^B = 35,000$.

We start by assuming $n^A = 0.22$ for the first simulation and then increase the value by 0.02 in three subsequent rounds. Figure 7 illustrates the results. The relevant value of n^A is reported in the figure's legend, together with the Nash equilibrium approximate values of prices.

Since no closed form solution exists for $p^{c*}(p^{-c})$, in Figure 7 best responses are approximated by a discrete number of numerical solutions. In Figure 7a, country A's best response lies below country B's, leading to a Nash equilibrium where $p^A = r^A$ and country B responds optimally. Consistent with the results of section 4.3, an initial increase in n^A shifts country A's and B's best responses respectively upwards and downwards. Increasing n^A from 0.22 to 0.24 (Figure 7b) implies a move from an equilibrium where country A is at a corner solution to one where it is at an interior solution (Corollary 1). A further increase (Figure 7c) increases the Nash equilibrium price for country A further (Proposition 3), still keeping both prices above their respective reservation levels. Finally, with a further increase in n^A, country B's price is at a corner, with country A responding optimally (Figure 7d).

B Appendices: empirical analysis

B.1 Diseases and products

Table 3 lists the 28 different neoplasm causes available in the GBD 2015 data set for which prevalence data are available.

Out of the original 108 antineoplastic drugs available, our final sample includes 83. These are listed in Table 4, together with the number of adopting countries for each product. Six of the excluded drugs do not treat cancer, 3 treat some types of cancer for which prevalence data are not available from our source, two 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 authorised drug, but differs on some other characteristics such as strength, indication or pharmaceutical form). In addition, ten were not on patent in any country in our sample during the period of analysis; in such cases, price may be affected by generic competition, which is not accounted for in our theoretical model. Two 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.

B.2 Robustness checks for the empirical analysis

In Table 5 we provide the results for the same analysis reported in Table 2, conducted on the untrimmed sample. With this sample, the optimisation procedure based on the cross validation criterion leads to select a polynomial of degree four: results are presented in columns (3) and (4). Figures 8 and 9 replicate what was shown for the baseline sample in Figures 5 and 6 of the main text. The results are qualitatively very similar.

Bladder cancer	Leukemia	Ovarian cancer
Brain and nervous system cancer	Lip and oral cavity cancer	Pancreatic cancer
Breast cancer	Liver cancer	Prostate cancer
Cervical cancer	Malignant skin melanoma	Stomach cancer
Colon and rectum cancer	Mesothelioma	Testicular cancer
Esophageal cancer	Multiple myeloma	Thyroid cancer
Gallbladder and biliary tract cancer	Nasopharynx cancer	Tracheal, bronchus and lung cancer
Hodgkin lymphoma	Non-Hodgkin lymphoma	Uterine cancer
Kidney cancer	Non-melanoma skin cancer	
Larynx cancer	Other pharynx cancer	

Table 3: List of neoplasm causes, as identified by the Global Burden of Diseases database 2015.

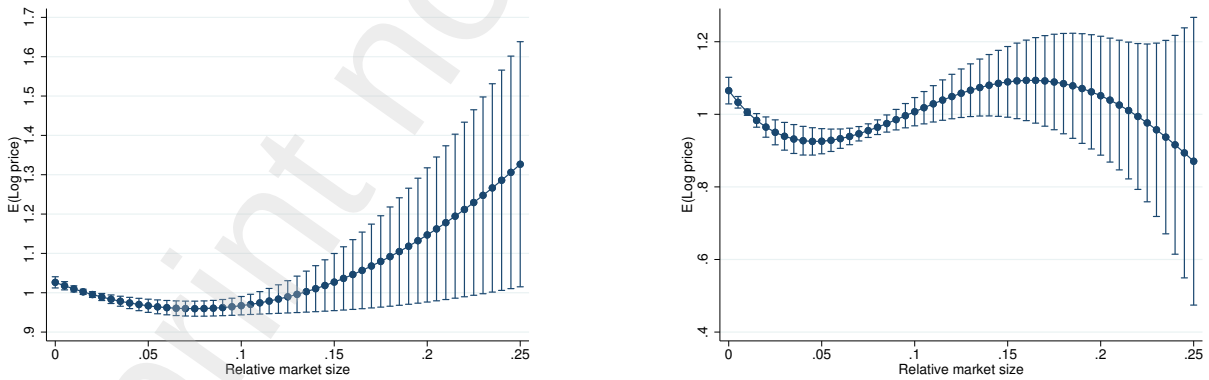
Product	Number of countries	Product	Number of countries	Product	Number of Countries
Abraxane	12	Iclusig	13	Sutent	22
Adcetris	17	Imbruvica	16	Tafinlar	20
Afinitor	20	Imlygic	7	Tagrisso	10
Arzerra	16	Inlyta	21	Tarceva	21
Atriance	16	Iressa	19	Targretin	2
Avastin	19	Jakavi	21	Tasigna	21
Blincyto	12	Javlor	13	Temodal	2
Bosulif	17	Jevtana	19	Teysuno	14
Cabometyx	5	Kadcyla	20	Torisel	18
Caprelsa	18	Keytruda	18	Trisenox	18
Cometriq	8	Kisplyx	5	Tyverb	20
Cotellic	10	Kyprolis	15	Unituxin	1
Cyramza	15	Lenvima	14	Vargatef	13
Dacogen	15	Litak	1	Vectibix	21
Darzalex	10	Lonsurf	10	Velcade	16
Depocyte	2	Lynparza	15	Venclyxto	7
Empliciti	8	Mabthera	21	Vidaza	16
Erbitux	20	Mekinist	11	Votrient	22
Erivedge	13	Nexavar	22	Xalkori	19
Evoltra	1	Ninlaro	5	Xaluprine	11
Farydak	9	Onivyde	1	Xeloda	2
Foscan	1	Opdivo	18	Yervoy	21
Gazyvaro	18	Perjeta	18	Yondelis	17
Giotrif	21	Pixuvri	9	Zaltrap	16
Glivec	1	Portrazza	6	Zelboraf	19
Halaven	16	Spectrila	2	Zydelig	15
Herceptin	21	Sprycel	22	Zykadia	14
Ibrance	9	Stivarga	18		

Table 4: Products included in the sample, together with the number of adopting countries.

	Dependent variable: ln(price per mg)			
	(1)	(2)	(3)	(4)
Relative market size	-1.410***	-1.790***	-6.715***	-6.959***
	(0.464)	(0.494)	(2.476)	(2.499)
Relative market size (squared)	9.422**	11.962***	109.065**	106.300**
	(3.965)	(4.241)	(52.777)	(52.291)
Relative market size (cubed)			-549.474	-491.176
			(373.037)	(364.247)
Relative market size (to the power 4)			836.237	659.454
			(836.625)	(810.368)
Natural logarithm of GDP per capita	0.165***	0.157***	0.146***	0.138***
	(0.019)	(0.019)	(0.019)	(0.019)
Natural logarithm of pharmaceutical export	0.019***	0.022***	0.021***	0.025***
	(0.002)	(0.002)	(0.002)	(0.002)
Number of years since launch date		-0.024***		-0.024***
		(0.004)		(0.004)
Number of observations	20155	20155	20155	20155
U-shape test ($p - value$)	0.019	0.007		
Extreme point	0.075	0.075		

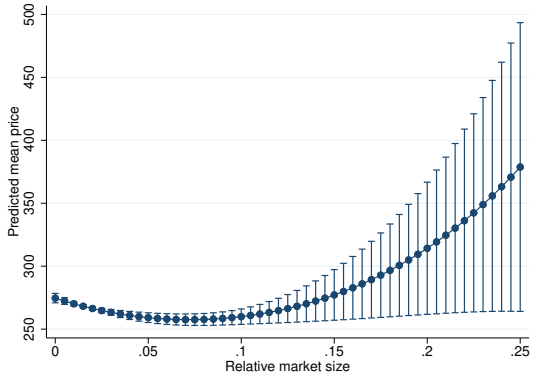
Models include product-level fixed effects.
Standard errors (in parentheses) are clustered at the product level.
* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 5: Results of the main empirical analysis. Untrimmed sample.

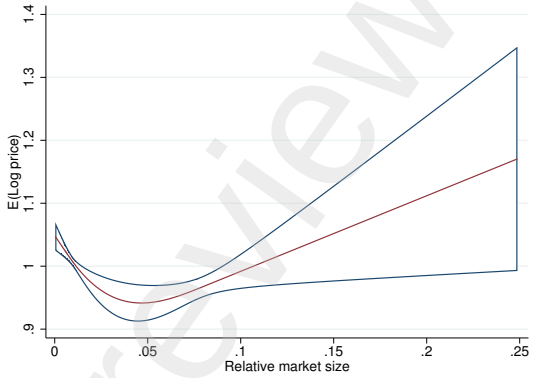


(a) Second-degree polynomial. **(b)** Fourth degree polynomial.

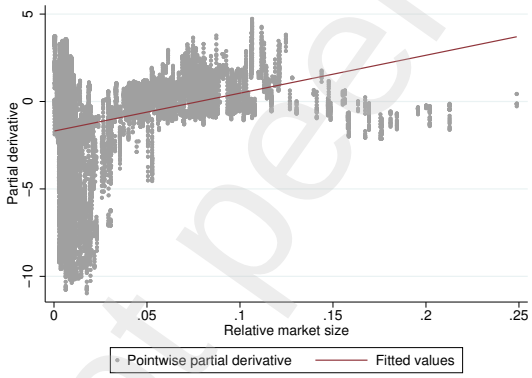
Figure 8: The relationship between price and relative market size for the models presented in columns (2) and (4) of Table 5. Predictive margins with 95% CI. Untrimmed sample.



(a) GLM, 2nd degree polynomial. Predictive margins with 95% CI.



(b) Cubic spline. Predictive margins with 95% CI.



(c) KRLS

Figure 9: The relationship between price and relative market size using three alternative models. Untrimmed sample.