Strategic Interaction in Pharmaceutical Price Regulation and Innovation

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Abstract

We present a model of the strategic interaction among authorities regulating pharmaceutical prices in different countries, and the resulting global investment decisions of pharmaceutical firms. Regulators’ decisions affect consumer surplus directly via prices and indirectly through the effect of price changes on firms’ profits and hence R&D investment decisions, which in turn affect patient health. The positive externality of a price increase in one country provides an incentive for other countries to free-ride. We study how relevant characteristics at the country level can affect optimal decisions by regulators and the possible equilibria. The theoretical predictions of the model will be tested using data on prices of a set of 108 cancer drugs in 25 countries.

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1 Introduction

According to the World Health Organisation, achieving fair pricing in health care systems, ensuring their long-term sustainability and securing access for patients, is one of the biggest challenges facing health care systems worldwide (WHO, 2015). Sustainability is a particular challenge, as health care expenditure growth outstrips GDP growth across the developed world. With a general consensus that technological innovation plays a central role in driving increased costs (Weisbrod, 1991), much effort has been targeted towards the process by which new health technologies are adopted and priced.

Somewhat surprisingly, as health care insurers have grown more concerned about technology-induced expenditure growth, suppliers of innovation have witnessed a substantial reduction in the number of new drugs approved per $bn spent on R&D. Munos (2009) reports that the rates of production of new drugs in recent years have been similar to those of the 1950s. When considered alongside the steady increase in R&D investment by the pharmaceutical industry, it is estimated that the number of new drugs approved per $bn spent on R&D has halved roughly every nine years since 1950 (Scannell et al., 2012). Such observations are supported by the work of DiMasi et al. (2003, 2016), who found evidence of an increasing trend in the average R&D cost of new drugs, and Pammolli et al. (2011), who found that R&D productivity of the pharmaceutical industry has been falling since 1990. If productivity is falling, no matter what the determinants are, understanding the link between regulation and R&D investment is of paramount importance: regulation could be an essential policy tool to secure innovation for the future.

The tension between regulating drug prices so as to ensure that medicines are available to patients, and at the same time incentivising long-term R&D for pharmaceutical innovation, is the well-known trade-off between static and dynamic efficiency (Leibenstein, 1966). While the majority of studies of pharmaceutical price regulation focus on the static dimension, interest in the relationship between the two dimensions is growing. For example, the welfare implications of the adoption of price regulation is studied in Filson (2012), and other contributions to the literature focus on specific types of regulation, such as cost-effectiveness thresholds (Jena and Philipson, 2008), value-based pricing (Danzon et al., 2015) and risk-sharing agreements (Levaggi et al., 2017). A key observation is that the institutional features of the health care system may play an important role in determining the actual impact of a policy.

One strand of literature studies the effect of health insurance coverage on drug pricing, innovation and welfare. For example, Lakdawalla and Sood (2009) study the static and dynamic efficiency effects of public drug insurance for a market in which new drugs are provided under patent protection and generics are supplied in a competitive setting. Bardey et al. (2016) study the effect of a regulator’s optimal choice of copayments and reference pricing on equilibrium prices and supply in an imperfectly competitive drugs market. A separate strand of literature investigates the relationship between public funding of pharmaceutical research and the degree of pharmaceutical innovation. Using longitudinal data on U.S. National Institutes for Health (NIH) extramural research funding between 1975 and 2006, Blume-Kohout (2012) estimated that a ten per cent increase in targeted NIH funding leads to a 4.5 per cent increase in drugs entering clinical testing, but found no evidence that such funding leads to an increase in the number of phase III clinical trials. Tooì (2007) used a panel data set from the NIH to investigate the impact of
public basic and clinical research in seven medical classes on pharmaceutical R&D investment over a period of 18 years. They found strong evidence that public and private research are complements, that the degree of uncertainty in public research funding affects the timing and size of private investment and that, in the presence of price controls, private R&D investment declines. Kyle et al. (2016) considered how medical research funding of one government responds to R&D spending of another. Using data from the NIH between 2007 and 2014, they found that a 10% increase in U.S. government funding for infectious and parasitic diseases leads to a 1% reduction in funding by other funders in the following year and a 4% reduction of the aggregate spend of other governments. The authors interpret the results as evidence that other countries free-ride on the United States in terms of research funding. However, the reasons why the United States and the rest of the world seem to have a different strategic position are not investigated.

The majority of this literature adopts the perspective of a single country acting independently of other countries. A peculiarity of the pharmaceutical market is that it is a global market with extensive regulation at country level. Hence global profits and R&D decisions are strongly influenced by local decisions made across a wide range of jurisdictions. As a result, there can exist externalities, in that policies adopted in one country may impact on the policy decisions of other countries, thereby creating the potential for strategic interaction among regulators. In this respect, pharmaceutical policies may be seen to be similar to policies in other fields that have been extensively studied, where externalities are important. The best known field is probably that of environmental policies with global impacts, such as those designed to tackle global warming. Another example 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, by attracting capital and reducing the tax base (see, for example, the seminal paper by Zodrow and Mieszkowski (1986)). Theory predicts the so-called ‘race to the bottom’ of capital income tax rates, and an under-provision of public goods. Another example is the strategic interaction among different countries in designing tariff policies, due to the negative externality associated with a tariff set in one country on the exporter’s terms of trade (Beshkar et al., 2015).

In contrast to these two cases, the analysis of strategic interaction in the regulation of the pharmaceutical industry, with its concomitant effect on global R&D investments, has received very limited attention so far. The present paper develops a theoretical model of strategic interaction among different countries in setting regulated prices for pharmaceuticals. The model aims to capture the key characteristics required for the welfare analysis of drug markets when local factors such as country-level pharmaceutical reimbursement policies, disease burdens and willingness to pay impact global pharmaceutical innovation. It shows how regulators’ pricing policies affect welfare, directly through their impact on consumption, and indirectly by providing firms with incentives to invest in R&D that can improve the quality of products available to patients. In the empirical analysis, we study the determinants of pricing exploiting a multi-product and multi-country dataset. In particular, the analysis focuses on branded cancer drugs approved by the European Medicines Agency. For these drugs, quarterly ex-factory prices, net of mandatory rebates, have been retrieved for 25 OECD countries over the period 2007-2017 from the Pricing Insights IMS database. We believe that ours is the first contribution which models the strategic interaction among countries, taking both static and dynamic implications of pricing policies into account.
Most closely related to our work is that of Filson (2012), who investigated the welfare properties of pharmaceutical price regulation and concluded that consumers in the U.S. tend to be better-off with market prices: the long-term losses in dynamic efficiency that would arise from regulation outweigh the short-term gains in static efficiency that regulation brings. In his framework, firms act to maximise profits given the set of exogenous price caps imposed in a group of countries. The welfare analysis is then based on the comparison of equilibria implied by different combinations of policies by countries. Filson’s baseline parametrization suggests that countries other than the United States, where prices are typically regulated, free ride on U.S. willingness to support market prices. As a result, global consumer welfare would increase if other countries would abandon price regulation. The fact that policies are taken to be exogenous in Filson’s work prevents the study of whether different countries may be more or less willing to free ride on others.

Section 2 presents a simple two-country model of strategic interaction in pharmaceutical pricing and innovation. In section 3, we study optimal investment and pricing policies for a ‘first best’ situation, in which there exists a single world regulator responsible for choosing pharmaceutical prices in each country, and under decentralised price setting. Section 4 discusses the efficiency and policy implications, referencing current EU policies on joint procurement. Section 5 presents our empirical model and section 6 concludes.

2 The model

We model two countries, A and B, in which a single profit-maximising firm is selling a drug. In each country there is a regulator which is responsible for maximising welfare by setting the prices, \( p^A \) and \( p^B \), to be paid for the drug. The number of patients who can benefit from the drug are \( N^A > 0 \) and \( N^B > 0 \). The firm faces country-specific market access costs and has concerns about parallel trading between the two countries, should one of the two prices be sufficiently lower than the other. This leads the firm to set reservation prices \( r^A \geq c \) and \( r^B \geq c \), where \( c > 0 \) is the marginal cost of production. If the price proposed by the regulator falls below the reservation price for that country, the firm will not sell the drug in that country.

The country-specific individual-level inverse demand functions are downward-sloping and linear, with common slopes equal to \( -b \), \( b > 0 \), and common intercepts equal to \( \delta \). \( \delta \) is function of the firm’s total level of R&D investment in the drug, \( I \geq 0 \), such that a higher level of investment increases \( \delta \) but at a decreasing rate (that is, \( \delta_I > 0, \delta_{II} < 0, \delta(0) = 0, \delta_I(0) > 0 \)). The dependency of \( \delta \) on \( I \) is meant to describe the impact of R&D investments on the effectiveness of the drug, and therefore on the willingness to pay for it.

Define the patient-level marginal willingness to pay (MWTP) functions in countries \( i = A, B \) as:

\[
\text{MWTP}^i = \kappa^i \delta(I) - bq^i, \quad i \in \{A, B\},
\]

In principle, reservation prices may depend on some of the variables on which optimal prices, conditional on adoption, depend. We do not model this dependency.
where $q^i$ is quantity and we allow for differences in the way the two countries value the drug by using the scaling factor $\kappa^i$ on $\delta$. The individual demand functions are:

$$q^i(p^i) = \frac{\kappa^i \delta(I) - p^i}{b}, \quad i \in \{A, B\}.$$  

(2)

This specification assumes that 100% of the cost of the drug is reimbursed by the regulator, an assumption which ignores the role of co-insurance. We discuss this assumption in more detail in section 6. For brevity, we drop the dependence of $I$ on $p^A$ and $p^B$ in the following.

Define the profit function of the firm as:

$$\Pi(\beta) = 1_{p^A \geq r^A} \frac{N^A(p^A - c)(\kappa^A \delta(I) - p^A)}{b} + 1_{p^B \geq r^B} \frac{N^B(p^B - c)(\kappa^B \delta(I) - p^B)}{b} - I,$$  

(3)

where $\beta \equiv (N^A, N^B, c, b, \kappa^A, \kappa^B, r^A, r^B)$ and $1_F$ is an indicator function that is equal to 1 if the event $F$ holds and zero otherwise. The welfare functions of the two countries may then be defined as follows:

$$W^A(p^A, I(\beta); \beta) \equiv \alpha^A CS^A(\cdot) + (1 - \alpha^A)\lambda\Pi(\cdot),$$  

(4a)

$$W^B(p^B, I(\beta); \beta) \equiv \alpha^B CS^B(\cdot) + (1 - \alpha^B)(1 - \lambda)\Pi(\cdot),$$  

(4b)

where $CS^i$ is consumer surplus in country $i$:

$$CS^i = N^i \int_{p^i}^{\kappa^i \delta(I)} q^i(p^i) dp^i = \frac{N^i}{2b} \left[ \kappa^i \delta(I) - p^i \right]^2.$$  

(5)

$\alpha^i \in [0, 1]$ is the weight given to consumer surplus relative to profit in the welfare function and $\lambda \in [0, 1]$ is the fraction of global profits accruing to country $A$. $\lambda$ accounts for the fact that, although pharmaceutical companies operate in a global market, the location of their operations affects the destination of their profits.

To solve for the optimal pricing policy of the regulators and the optimal investment choice of the firm, the order of events is assumed to be the following. Firstly, the optimal levels of $p^A$ and $p^B$ are chosen simultaneously by the regulators in countries $A$ and $B$. Then $I$ is chosen by the firm so as to maximise profits. Although it may be argued that investment decisions are made before prices are fixed, we assume that current prices affect the firm’s expectations of future prices, and therefore future profits. This allows us to study the key mechanism at work, while reducing the level of complexity of the model.

3 Optimal investment and pricing policies

In this section, we set a benchmark by studying a first-best solution in which a single regulator maximizes welfare over both countries. We then analyse the decentralized solution. Optimal policies for pricing and investment are established by working recursively, given the above assumption that prices are chosen prior to investment. We therefore start by defining the firm’s optimal investment policy, which is a function of the prices chosen by the regulator (or regulators) and is therefore independent of whether we study the first-best or the decentralized model.
3.1 The firm’s optimal investment policy

Given that \( p^A \) and \( p^B \) have been optimally chosen by the regulator(s), the firm solves:

\[
\max_I \left\{ 1_{p^A \geq r^A} N^A (p^A - c) q^A + 1_{p^B \geq r^B} N^B (p^B - c) q^B - I \right\},
\]

where \( q^A \) and \( q^B \) are defined in Eq. (2). The first order necessary condition for the optimal level of \( I^* > 0 \) is:

\[
\delta_I(I^*) = b = 1_{p^A \geq r^A} N^A (p^A - c) + 1_{p^B \geq r^B} N^B (p^B - c).
\]

According to Eq. (7), \( I^* \) is an increasing function of the prices set in both countries. Hence the overall level of welfare in each country depends not only on the price chosen by that country’s regulator, but also on the price chosen by the regulator of the other country, via the effect of price-setting on investment and, in consequence, marginal willingness to pay.

3.2 First Best

As a benchmark against which to judge later cases, consider a model in which there exists one regulator responsible for choosing prices \( p^A \) and \( p^B \) so as to maximise \( W^A + W^B \). In this case, the regulator solves the following problem:

\[
\tilde{W} = \max_{p^A, p^B} \alpha^A 1_{p^A \geq r^A} CS^A (I^*, p^A) + \alpha^B 1_{p^B \geq r^B} CS^B (I^*, p^B) + [1 - \alpha^B + \lambda (\alpha^B - \alpha^A)] \Pi(I^*),
\]

where, according to Eq. (7), \( I^* \) is a function of \( p^A \) and \( p^B \). The first order condition for the choice of \( p^A \geq r^A \) is:

\[
\tilde{W}_{p^A} = \frac{\alpha^A N^A}{b} \left( \kappa^A \delta(I^*) - p^A \right) \left( \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} - 1 \right) + \frac{\alpha^B N^B}{b} \left( \kappa^B \delta(I^*) - p^B \right) \kappa^B \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^B} \\
+ [1 - \alpha^B + \lambda (\alpha^B - \alpha^A)] N^B q^B \left( 1 + \epsilon^A \frac{p^A - c}{p^A} \right) \leq 0,
\]

\( (p^A - r^A) \geq 0, (p^A - r^A) \tilde{W}_{p^A} = 0, \)

where \( \epsilon^A \) denotes the price elasticity of demand in country A at the optimal price.

A similar condition applies to country B:

\[
\tilde{W}_{p^B} = \frac{\alpha^B N^B}{b} \left( \kappa^B \delta(I^*) - p^B \right) \left( \kappa^B \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^B} - 1 \right) + \frac{\alpha^A N^A}{b} \left( \kappa^A \delta(I^*) - p^A \right) \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} \\
+ [1 - \alpha^B + \lambda (\alpha^B - \alpha^A)] N^A q^A \left( 1 + \epsilon^B \frac{p^B - c}{p^B} \right) \leq 0,
\]

\( (p^B - r^B) \geq 0, (p^B - r^B) \tilde{W}_{p^B} = 0, \)
For an interior solution to exist, for example, for \( p^A \), Eq. (8) implies:

\[
\tilde{W}_{p^A} = \alpha^A N^A q^A \left( \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} - 1 \right) + \alpha^B N^B q^B \kappa^B \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A}
\]

\[
+ [1 - \alpha^B + \lambda (\alpha^B - \alpha^A)] N^A q^A \left( 1 + \epsilon A \frac{p^A - c}{p^A} \right) = 0.
\]

The first line of Eq. (10) is the net marginal benefit of an increase in the price in country A on the sum of consumer surplus in both countries: increasing \( p^A \) shifts the demand curve upwards in both countries, but only in country A is there an offsetting effect on consumer surplus due to the higher price faced by consumers. The term on the second line of Eq. (10) is the net marginal benefit of an increase in \( p^A \) on global profit accruing to country A, appropriately weighted. When an interior solution for \( p^B \) exists, the interpretation is the same for Eq. (9).

If the reservation prices \( r^A \) and \( r^B \) are binding, the drug may be reimbursed at the reservation price or not be reimbursed \((p = 0)\), depending on which solution makes total welfare greater.

### 3.3 Decentralised price setting

The two regulators face the same problem: to choose the optimal price in their own country, knowing that the other regulator shall do likewise, and knowing that the firm will follow an optimal investment policy conditional upon the two prices that are chosen. Here we state the problem faced by the regulator in country A; a similar approach applies for the regulator in country B. Since the firm’s optimal investment policy is independent of who actually sets the prices, Eq. (7) is still valid for the definition of the optimal investment level of the firm.

Referencing Eqs. (3) and (4a), write country A’s welfare function as follows:

\[
W^A = \frac{\alpha^A N^A}{2b} \left[ \kappa^A \delta(I^*) - p^A \right]^2 + \left( 1 - \alpha^A \right) \lambda \left[ \frac{N^A (p^A - c) (\kappa^A \delta(I^*) - p^A)}{b} \right]
\]

\[
+ \frac{N^B (p^B - c) (\kappa^B \delta(I^*) - p^B)}{b} - I^*,
\]

where \( I^* \) is defined according to Eq. (7). The regulator in country A solves:

\[
\max_{p^A} W^A(p^A, I^*(p^A; \beta); \beta).
\]

Under the assumptions that were made on the shape of the demand function and \( \delta(I) \), both the consumer surplus and the profit functions are concave in \( p^A \). Therefore the weighted sum of them is also concave (Léonard and Van Long [1992], Theorem 1.1.2). This ensures the existence of a maximum for \( W^A \).

The first order condition for the optimal price in country A, given the price in country B, is:

\[
W_{p^A}^A = \frac{\alpha^A}{b} (\kappa^A \delta(I^*) - p^A) \left( \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} - 1 \right) + \left( 1 - \alpha^A \right) \lambda \left( \kappa^A \delta(I^*) + c - 2p^A \right) \leq 0,
\]

\[
(p^A - r^A) \geq 0, (p^A - r^A) W_{p^A}^A = 0.
\]
A comparison of Eq. (13) with Eq. (8) highlights two spillover effects which only exist when welfare over both countries is maximised. The first (the second term on the RHS of Eq. (8)) refers to the impact that a price change in one country has on the consumer surplus of the other, via the effect that the price change has on $I^*$ and, correspondingly, marginal willingness to pay in the other country. The second effect is related to the impact of a change in the price in one country on firm profits accruing to the other country. These spillover effects underpin the potential for free-riding of some countries on others, as discussed in some of the existing literature.

Assuming an interior solution for $p^A$, to interpret this first order necessary condition it is useful to consider the derivatives of $CS^A$ and $\Pi$ with respect to $p^A$ separately. Considering first the derivative of $CS^A$ with respect to $p^A$ (the first term on the RHS of Eq. (13)), the term $\kappa^A \delta(I^*) - p^A$ is the distance between the intercept of the MWTP function and the price. This must always be positive if $CS^A$ is to be positive. Hence, the derivative of $CS^A$ with respect to $p^A$ will equal zero when:

$$\kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} = 1.$$  \hfill (14)

That is, at the margin, the indirect (positive) effect that the price increase has on MWTP via the firm’s optimal choice of $I^*$ (see Eq. (7)) is equal to the direct (negative) effect of an increase in price on $CS^A$.

Considering the derivative of $\Pi$ with respect to $p^A$ in Eq. (13), after application of the Envelope theorem to eliminate the partial derivative of $I^*$ on profit, we are left with the standard monopolist’s rule equating marginal cost to marginal revenue. In a standard model of a profit-maximising monopolist, the trade-off between consumer-surplus maximization and profit maximization is clear: any increase in price above marginal cost increases profits and reduces consumer surplus. However, in our model, a price increase effects an upward shift of the demand function via the incentive to invest in R&D. The welfare-maximizing price chosen by the regulator can therefore be seen as a weighted average of the consumer surplus and pure profit maximizing prices. Other things being equal, the weight on the consumer surplus component is larger the larger is the value of $\alpha$ and the larger is the fraction of the profits accruing to country $A$ (the larger is $\lambda$).

A useful way to see how these effects interact is to derive an adjusted version of the Lerner index for our problem for any interior solution defined by Eq. (13):

$$\frac{p^{A*} - c}{p^{A*}} = -\frac{1}{\epsilon^A \lambda} \left[ \lambda + \frac{\alpha^A}{1 - \alpha^A} \left( -1 + \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} \right) \right].$$ \hfill (15)

The final two terms in Eq. (15) are the weighted adjustments which account for the aforementioned marginal impact of price on consumer surplus: the direct effect on consumer surplus and the indirect effect resulting from an upward shift in the demand function via the incentive to invest in R&D. This expression collapses to the standard Lerner index for a monopolist when only profits matter for welfare ($\alpha^A = 0$).

It is straightforward to use the implicit function theorem to show that, if the interior solution for $p^{A*}$ lies below $p^M$, where $p^M$ is the profit-maximising price, the optimal choice of $p^{A*}$ is
higher the lower is the weight placed on consumer surplus ($\alpha^A$) and the larger is the share of the industry profits accruing to country A ($\lambda$) (see Section A in the Appendix).

The attention so far has been restricted to interior solutions. In the absence of an interior solution, two thing may happen. If the value of welfare in the country with $p^A = r^A$ is positive, then the product will be reimbursed at the reservation price. If it is negative, the drug will not be reimbursed.

### 3.4 Strategic interaction

In this section we study the properties of the reaction functions derived in Section 3.3 and the resulting equilibria when the pricing policy in each country affects the optimal pricing policy of the other country. We start by considering a special case of the welfare function in which only consumer surplus matters ($\alpha = 1$). This is interesting in itself, but is also useful to understand the results for model in which both consumer surplus and profits matter.

#### 3.4.1 Only consumer surplus matters

Let $\alpha^A = 1$ and $\alpha^B = 1$, so that welfare each country depends only on consumer surplus in that country. In this case, the reaction functions are linear with slopes which depend on the relative size of the number of patients in the two countries, weighted by the respective value of $\kappa$. In particular,

$$ \left. \frac{dp^A}{dp^B} \right|_{\alpha^A=1} = -\frac{N^B \kappa^B}{N^A \kappa^A}. \tag{16} $$

According to Eq. (16), if regulators are only concerned about CS, prices are strategic substitutes and reaction functions are linear. The firm’s investment decision depends on total profit regardless of the country of origin. Hence each country reacts to an increase in price in the other country with a decrease in own country prices, because its consumer surplus can be increased by reducing prices, while the optimal level of investment remains constant thanks to the policy undertaken in the other country. Moreover, since

$$ \left. \frac{dp^B}{dp^A} \right|_{\alpha^B=1} = -\frac{N^A \kappa^A}{N^B \kappa^B}. \tag{17} $$

the reaction functions are parallel. This situation is illustrated in Figure 1. Assuming that the drug is reimbursed in both countries ($p^A \geq r^A$ and $p^B \geq r^B$), only one Nash equilibrium exists (Hoel, 1991), where the price equals the reservation price in one country and the other country reacts optimally. This corresponds to point NE in the figure. In the example illustrated in Figure 1, country B sets the price at its reservation price, whereas the price in country A strictly exceeds $r^A$. With two perfectly symmetric countries, the two reaction functions overlap, leading to multiple equilibria (see, Finus (2001)).

#### 3.4.2 The general case

Now consider the case when profits can enter the welfare function of each country (that is, $0 \leq \alpha^A < 1$ and $0 \leq \alpha^B < 1$). We study the results for country A, noting that similar conclusions
may be drawn for country B. The implicit function theorem can be applied to Eq. (13) when there exists an interior solution, to obtain an expression for the reaction function’s slope, $dp^A*/dp^B$:

$$
\alpha^A \left[ \kappa^A \frac{\partial \delta^A}{\partial I^*} \frac{\partial I^*}{\partial p^A} - 1 \right] + \kappa^A \left( \frac{\partial^2 I^*}{\partial p^A \partial p^B} + \frac{\partial \delta^A}{\partial p^A} \frac{\partial I^*}{\partial p^A} \frac{\partial I^*}{\partial p^B} \right) (\kappa^A \delta(I^*) - p^A) + \frac{(1-\alpha^A)\lambda N^A}{\kappa^A} \left( \frac{\partial \delta^A}{\partial I^*} \frac{\partial I^*}{\partial p^B} \right).
$$

(18)

For the case of pure profit maximization ($\alpha^A = 0$), it can be shown that prices are strategic complements. The mechanism at work in this case is also straightforward: an increase in price in the other country increases MWTP and hence marginal revenue in the own country via its impact on $I$, meaning that the profit maximizing price is higher. Hence, the contribution to the reaction function of the profit maximizing objective goes in the opposite direction with respect to the CS maximization objective. Overall, in the general case ($0 < \alpha^A < 1$), reaction functions could be increasing or decreasing and might be non-monotonic.

Finding an analytical solution to Eq. (13) is hard, even if an explicit functional form is assigned to $\delta(I)$. In what follows, we illustrate graphically some reaction functions and equilibria, based on numerical solutions of a simulation which assumes that $\delta(I) = \ln(I)$. Table 1 summarizes the parameter values for a baseline case and variations in which some parameters for country A are changed, holding those in country B constant.

In the baseline case, country A differs from country B in the following ways: it has a smaller population (50 vs. 70), a lower willingness to pay for the innovation (15 vs. 25), a larger share of the industry profits accruing to the country (0.7 vs. 0.3). The weight for profit in each welfare
Table 1: Parameter values for the simulation

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The smaller size of the population in country A explains why $p^A$ is more sensitive to changes in $p^B$ than $p^B$ is to changes in $p^A$ (see Eq. (16)). In this baseline case, there exists a unique Nash equilibrium, with $p^A < p^B$. This is mainly the result of the larger size of the population in country B ($N^B > N^A$) and the higher willingness to pay ($\kappa^B > \kappa^A$). These two effects together more than offset the impact of the larger fraction of industry profits accruing to country A ($\lambda > 0.5$).

Figures 2(b) to 2(d) show the reaction functions and equilibria for the scenarios corresponding to columns two to four in Table 1. For these additional cases, a unique Nash equilibrium exists, in which both countries set prices strictly greater than their respective reservation prices. According to the figures, an increase in $\kappa^A$, in $N^A$, and $\lambda$, holding the other parameters fixed, shifts country A’s reaction function upwards. However, it does not necessarily follow that $p^A$ increases in the Nash equilibrium, because a change in the parameter value for one country changes the position of the other country’s reaction function (see Eq. (18)). For example, a comparison of Figures 2(a) and 2(b) shows that an increase in $\kappa^A$ shifts the intercept on the horizontal axis of the reaction function $p^B(p^A)$ to the right, which has an offsetting effect on the equilibrium value of $p^A$.

Concerning the impact of an increase in $\lambda$, Figure 2(d) shows that, as expected, country A’s reaction function becomes flatter and departs from linearity, in comparison with the previous figures. As was noted in discussing Eq. (18), the consumer surplus maximization component of the welfare function leads to linear and negatively-sloped reaction functions. On the other hand, prices are strategic complements in the profit maximising component of the welfare function, that is, when $\alpha = 0$, we would obtain positively sloped reaction functions. As a result, a larger weight of profits in the objective function makes country A’s reaction function flatter.

So far, our focus has been on combinations of parameters such for which there exists a unique Nash equilibrium such that $p^A > r^A$ and $p^B > r^B$. However, this need not be the case. For example, Figure 3 shows the reaction functions that are obtained by keeping all parameter values at their baseline values, but increasing the value of $N^A$ to 90. As for the case where only consumer surplus matters in the welfare function (see Figure 1), the reaction functions do not cross. There
exists only one Nash equilibrium, where country B prices at $r^B$ (the origin of the horizontal axis in Figure 3) and country A responds optimally.

The possibility that an equilibrium exists where in one country the price is as low as the reservation price, and the strategic interaction leads the other country’s regulator to raise the price to provide incentives to invest in R&D, means that, in principle, the free-riding mechanism discussed in some of the literature may be relevant. Moreover, our theoretical model allows us to identify some of the characteristics that affect the incentive for single countries to act as free-riders. All this hinges on the assumption that regulators actually consider the long-term impacts of their pricing policies on pharmaceutical R&D investment when setting prices. Whether this is actually the case, is clearly an empirical question that we will try to address.

4 Efficiency and policy implications

A comparison of Eq. (8) with Eq. (13) highlights the efficiency implications of price setting at the individual country level. When a country sets its price to maximise its own welfare, it fails to
internalise the full positive impact on $\delta$ (owing to an increase in R&D investment), from which the other country will also benefit, as well as the impact on profits accruing to the other country. With reference to the former effect, this mechanism has the potential to provide an incentive to free-ride, as suggested by part of the literature. With free-riding, the price set by a single country will be below the level which maximises total welfare. An immediate implication is that total welfare could be enhanced by coordinating price setting mechanisms.

The model therefore provides a conceptual framework with which to analyse real world proposals to coordinate pricing policies. On 10 April 2014, the European Commission approved a Joint Procurement Agreement (JPA), which will enable all EU countries collectively to procure pandemic vaccines and other medical countermeasures. More generally, joint procurement of pharmaceuticals is feasible under European Directive 2014/24/EC on public procurement. Underlying the joint procurement proposal is the idea that it would lead to lower prices for single public authorities. This has also led to the creation of a European facility for the joint procurement of medical countermeasures in the context of cross-border health threats (i.e. communicable diseases). Interestingly, in 2015, the American Chamber of Commerce to the European Union issued a position paper calling for a 'more strategic use of procurement to stimulate innovation uptake’. The document claims that 'a more strategic assessment of value for money can be achieved to stimulate investment in innovation and foster effective, resilient and accessible health systems in Europe’. With reference to our model, the implementation of joint procurement in Europe would make the real world relationship between U.S. and Europe more akin to our two-country model described above. In the absence of joint procurement, each European country may be seen as a player of comparatively small size ($N_{\text{small}}$) in a global market with at least one big player (the U.S.). In a situation like this, a possible outcome of strategic interaction is that smaller countries price at reservation prices, with most of the effort to provide incentives to R&D left to larger countries (see, for example, Figure 3). The goal of joint procurement is the expectation that this allows to negotiate lower prices. In terms of parameters of our model this could be interpreted as a reduction in the reservation price: this would actually reduce prices, as
long as the constraint on reservation prices is binding. However, if dynamic efficiency considerations are taken into account in setting prices, the larger size of a single European contracting authority would also substantially change its strategic position. In particular, the larger population size might shift the reaction function upwards thus making a corner solution less likely to be an optimal response. The net impact of joint procurement on profits could then also be an increase in prices.

5 Econometric specification and data

In order to test the predictions from the theory and to estimate the impact of different variables on the prices set by regulators, we estimate the following log-linear model:

$$\log(P_{i,c,t}) = \alpha + \gamma \text{avg}(\log(P_{i,-c,t-1})) + \delta X_{i,c,t} + \zeta_i + \eta_c + \nu_t + \epsilon_{i,c,t},$$  \hspace{1cm} (19)

where $\log(P)$ is the natural logarithm of price, $i$ denotes the drug, $c$ denotes the country and $t$ denotes time. $\text{avg}(\log(P))$ is the natural logarithm of the average of the prices set in other countries, $X$ is a vector of time-varying regressors, $\zeta_i$ is a product fixed effect, $\eta_c$ a country fixed effect and $\nu_t$ a time fixed effect.

Drug prices may only be observed for products which are available in country $c$ at time $t$. It has been pointed out that price regulation has a significant effect in determining the extent and timing of new drugs launch, and that companies avoid price-controlled markets (Kyle, 2007). In our case, since regulation strategies within a country do not vary sharply over time, the selection process of a firm with respect to the entrance in a given market may be considered as time constant: the presence of country fixed effect therefore solves both the problem of unobserved heterogeneity between countries and the sample selection problem (Dustmann and Rochina-Barrachina, 2007).

The inclusion of $\text{avg}(\log(P_{i,-c,t-1}))$ allows us to measure the level of strategic interaction among countries, verifying the extent to which the price in country $i$ is affected by the lagged, average price set in other countries. Since the prices are jointly determined, $\text{avg}(\log(P_{i,-c,t-1}))$ is endogenous. To address this issue, we adopt an instrumental variable approach which uses as an instrument the weighted average of the control variables in the other countries (see for example Devereux et al., 2008).

We estimate the model using all 108 branded drugs in the Anatomic Therapeutic Chemical class L01 (Antineoplastic agents) that were approved by the European Medicines Agency (EMA) between January 1995, when the EMA was established, to April 2017. Generic and biosimilar drugs are excluded. Oncology therapies are chosen as a focus since, together with statins, they represent the two largest therapeutic classes in terms of sales value (OECD, 2008). Moreover, in recent years this therapeutic area has been characterised by some key innovations, with substantial impacts on survival and quality of life of patients. Finally, consistent with the theoretical model, the price of cancer drugs is heavily regulated by payers.

\textsuperscript{2}As pointed out above, prices depend mainly on demand side considerations. Indeed, R&D costs are sunk, so they do not influence actual market prices, while marginal costs, like production costs, are low and explain little about prices.
For these 108 drugs, quarterly prices for the period 2007-2017 have been retrieved for 25 OECD countries (their list is provided in Table 2 in Appendix B) from the Pricing Insights IMS database. We use ex-factory prices (the manufacturers’ posted prices) per standard unit, expressed in Euro, net of mandatory rebates.

The vector $X_{i,c,t}$ includes the log of the market size $N$, which is proxied by the number of individuals affected by each disease. Prevalence data are extracted from the Global Burden of Diseases (GBD) 2015 database and are provided for 29 different neoplasm causes (their list is provided in Table 3 in Appendix B). To match each drug $i$ with its market size, we consider the therapeutic indication reported by the EMA: according to this indication, each drug is matched to one or more of the 29 neoplasm causes identified by the GBD 2015. When drugs have more than one indication, prevalence is obtained as the sum of prevalences over all diseases with an indication. Since prevalence data are calculated over a five year period, the prevalence is considered to remain constant over that period.

$X_{i,c,t}$ also includes the following factors that are thought to determine pharmaceutical prices, according to previous literature:

- time since entering the market: as pointed out by Cabrales and Jiménez-Martín (2013); Kanavos and Vandoros (2011); Ekelund and Persson (2003); Lu and Comanor (1998); Comanor and Schweitzer (2007); Danzon and Chao (2000) among others, price premia are paid for new products. Indeed, new medicines are assumed to display improvements in their clinical profile compared with existing ones. Data on time from entry are retrieved for the Pricing Insights IMS database;

- competitive forces, proxied by the number of products for the same neoplasm cause already available in the market (see Ekelund and Persson 2003; Lu and Comanor 1998). This information is retrieved from the Pricing Insights IMS database. We follow the same approach mentioned for the market size to match each drug, according to its therapeutic indication, to one or more of the 29 neoplasm causes identified by the GBD in 2015. Our measure of competitive forces should not be distorted by the fact that our dataset includes only branded drugs: indeed, since we are only considering recent drugs, it is plausible to assume that they have no direct generic competitors yet;

- the natural logarithm of GDP per capita in 2000 US $ (as in Cabrales and Jiménez-Martín 2013), as a proxy for the ability to pay. These data are gathered from the World Bank Indicators;

- public and private health expenditure as a proportion of GDP (as in Cabrales and Jiménez-Martín 2013), both obtained from the WHO health database.

While a considerable body of empirical literature exists on the international comparison of drug prices and on the determinants of prices in individual countries, ours is among the few

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3 All the 25 countries included in the sample were already member of the OECD in 2007, the first year included in our analysis.
4 See OECD (2008), chapter 2, for an extensive review.
contributions which exploit cross-country data to study the determinants of pharmaceutical prices across different countries: other contributions in this field are Cabrales and Jiménez-Martín [2013], Kanavos and Vandoros [2011] (which consider 25 and 15 countries, respectively). The adoption of panel data makes the generalization of our results on the determinants of prices easier with respect to those found, for example, by Ekelund and Persson [2003] and Lu and Comanor [1998] for Sweden and the United States.

More importantly, in comparison with the existing empirical literature, our focus is more specific and theoretically based. Section 3.3 discusses some comparative statics results for the optimal pricing policy in one country, given the price level in the other country (rest of the world). Some of the variables that are shown to play a role in our theoretical analysis are also covariates of existing empirical works. For example, it seems reasonable to assume that the parameter $\kappa$ that affects the MWTP is related to measures like GDP per capita typically included as covariates. Our interest, however, is in the impact of variables that are peculiar to our model, and in particular, to the assumption that regulators interact in a global context and take long-term implications in terms of R&D incentives into account in setting prices. A key variable which is peculiar of our model is the size of the population targeted by the new technology. Hence, we expect that if dynamic efficiency implications of pricing policies are taken into account by rational regulators, pricing policies are affected by the size of the population to treat with that technology. If this happens, using the terminology used in other works, smaller countries free-ride on larger ones and, other things being equal, set lower prices. While the effect of global market size on pharmaceutical innovation has been largely analysed (see, for example, Kyle and McGahan [2012], Acemoglu and Linn [2003] and Dubois et al. [2015]), the role of prevalence at the national level as a determinant of pricing policies has not been studied yet. The introduction of $N$ represents therefore a fundamental peculiarity of our study with respect to Cabrales and Jiménez-Martín [2013]; Kanavos and Vandoros [2011]. More generally, while some contributions have considered the regulatory characteristics of the market, such as the explicit use of external reference prices (Kanavos and Vandoros [2011]), to the best of our knowledge no contribution has investigated to which extent the price in country $i$ is affected by the price set in other countries.

Finally, in terms of data, we are able to take into account the presence of mandatory rebates. This represents an important improvement in the literature on the determinants of pricing (Cabrales and Jiménez-Martín [2013]; Kanavos and Vandoros [2011]) since discounts or other incentives offered by manufacturers result in an effective price that is lower than the ex-factory price. For this reason, mandatory rebates are accounted for in some of the contributions focusing on international comparison of ex-factory prices (Danzon and Furukawa [2003] for example, estimate these discounts for the United States and report most of the results net of discounts), although also in this stream of literature discounts or rebates are usually ignored, since they are typically not disclosed.

Note that underlying our analysis is the assumption that greater profits made in one therapeutic area stimulate R&D investments in the same area.
6 Conclusion

The pharmaceutical industry is responsible for a large proportion of R&D investments on which the availability of future innovation depends. The willingness to invest in R&D is strongly related to the profits that companies expect to make, which in turn depend on prices and access to the market of innovations. The fact that prices in most countries are regulated, and regulation is specific to each country, implies a spillover effect: an increase in prices and profits in one country benefits all countries by inducing larger R&D investments and, as a result, creates more benefits for patients. The outcome of strategic interaction among countries may be an incentive for some countries to free-ride. For example, it has been suggested that countries might free ride on the higher prices allowed in the United States which stimulate R&D investment, while enjoying the benefits of lower prices in terms of patient access and expenditure burden.

To the best of our knowledge, this is the first paper to model explicitly this strategic interaction, with the aim of providing insights into how the specific characteristics of different countries affect their optimal policies. Using a two-country model, we first study which characteristics of one country affect its optimal pricing policy, given the prices set by the other. One crucial variable is the size of the population to treat, which, in most situations tends to increase the optimal level of prices. The key underlying mechanism is that an increase in prices in one country has a sizeable impact on the industry profits and hence on incentives to invest in R&D only if the size of the market is sufficiently large. Moreover, other things being equal, the sensitivity of optimal prices in the own country to changes in the other country is larger the smaller is the population size. In terms of equilibria, we show that there may exist equilibria where in one country the price is as low as the reservation price, and the strategic interaction leads the other country to raise the price to provide incentives to invest in R&D. This is a case where the free-riding mechanism discussed in some literature becomes particularly relevant.

We will use data on prices set for 108 cancer drugs in 25 OECD countries over the period 2007-2017 to test whether regulators interact in a global context and take long-term implications in terms of R&D incentives into account in setting prices.

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 a number of limitations that future research should aim to overcome. The most important observation is that there are other mechanisms that may affect the dependency of the optimal policy in one country on the policy adopted in other countries, such as external reference pricing and parallel trading. Ideally, these mechanisms should also be accounted for in the model. Furthermore, the model assumes that the drug is 100% reimbursed by the payer, who is also responsible for the definition of the level of demand. This assumption is more suited to some classes of drug than others. For example, insurance coverage tends to be higher for very costly drugs, which are often drugs targeting very severe health conditions and life threatening diseases. In these cases, payers actually play a key role in the definition of demand, by heavily regulating access to the technology. Lakdawalla and Sood (2009) investigate the role that insurance may play in mitigating the trade-off between static and dynamic efficiency, and an extension in this direction would be important for classes of drugs for which the patient’s decision is central in selecting the alternative for treatment. Finally, direct public investment in
R&D, as well as other policies that may affect investment decisions (such as tax regimes), could be incorporated into our framework.

References


A Comparative statics

Define \( \Psi(p^A_\ast, \beta) \equiv W^A_p \), where \( W^A_p \) is as defined in Eq. (13) and \( \beta \) is \( \alpha^A \) or \( \lambda \). Then, by the implicit function theorem, \( \frac{dp^A_\ast}{d\beta} = -\frac{\partial \Psi(\cdot)}{\partial \beta}/\partial \Psi(\cdot)/\partial p^A \), where \( \partial \Psi(\cdot)/\partial p^A \equiv W^A_p \). From this, \( \text{sign}(\frac{\partial p^A_\ast}{\partial \beta}) = \text{sign}(\partial \Psi/\partial \beta) \). When the welfare-maximising price lies below the profit-maximising price, the following results hold:

- for \( \alpha^A \):

  \[ \text{sign} \left( \frac{\partial p^A}{\partial \alpha^A} \right) = \text{sign} \left( q^A \left( \kappa^A \frac{\partial \delta}{\partial I^*} \frac{\partial I^*}{\partial p^A} - 1 \right) - \lambda (\kappa^A \delta(I^*(\cdot)) + c - 2p^A) \right) < 0. \]  
  \[ \text{(20)} \]

  The result follows because the final term in parentheses may be written as \(-\kappa^A \delta(I^*) + 2bq^A + c \) (using Eq. (1)), which is minus one times the marginal revenue evaluated at \( p^A_\ast \), plus marginal cost, which is strictly positive. Given this, the first term in parentheses must be strictly negative (refer to Eq. (13)). The result follows;

- for \( \lambda \), we use the same arguments. Hence:

  \[ \text{sign} \left( \frac{\partial p^A}{\partial \lambda} \right) = \text{sign} \left( \frac{1 - \alpha^A}{b} (\kappa^A \delta(I^*(\cdot)) + c - 2p^A) \right) < 0. \]

  \[ \text{(21)} \]

When the welfare-maximising price lies above the profit-maximising price, the signs in Eqs. (20) and (21) are reversed. Similar arguments may be used to show: \( \frac{\partial p^B_\ast}{\partial \alpha^B} < 0 \) and \( \frac{\partial p^B_\ast}{\partial \lambda} < 0 \).

B Additional material

Table 2: List of countries included in the sample.

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<tr>
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<th>Italy</th>
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Table 3: List of neoplasm causes, as identified by the GBD 2015.

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<th>Neoplasm Causes</th>
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<tbody>
<tr>
<td>Bladder cancer</td>
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<td>Brain and nervous system cancer</td>
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<td>Breast cancer</td>
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<td>Cervical cancer</td>
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<td>Colon and rectum cancer</td>
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<td>Esophageal cancer</td>
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<td>Gallbladder and biliary tract cancer</td>
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<td>Hodgkin lymphoma</td>
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<td>Leukemia</td>
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<td>Mesothelioma</td>
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<td>Multiple myeloma</td>
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