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Regulatory policy and the location of bio-pharmaceutical foreign direct investment in Europe☆

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ABSTRACT

This paper examines the relationship between cross-country differences in drug price regulation and the location of biopharmaceutical Foreign Direct Investment (FDI) in Europe. Simple theory predicts that price regulation in one country might affect total investment, but not the location of that investment, if sales are global. Nevertheless, some manufacturers threaten that the introduction of price regulation in a country will motivate them to move their investments to other countries. Are such threats cheap talk, or is there evidence that firms avoid price-controlling countries when making FDI location choices? We use data on 527 investments initiated in 27 European countries between 2002 and 2009 and find that investors are less likely to choose countries with price controls, after controlling for other determinants of investment. We also observe a relative decline in investment in countries that increased the stringency of regulatory regimes during our sample period. The effect is restricted to non-manufacturing investments and is most robust for those related to administrative functions.

1. Introduction

Pharmaceutical firms' decisions to invest abroad are at the center of public attention in Europe, as part of the broader debate over international outward investment. Can rich countries remain an attractive location for manufacturing firms when confronted with fierce competition from low-wage countries? A frequent response by economists to concerns about such off-shoring is that rich countries have a comparative advantage in high-tech skill-intensive industries, and that outflows of traditional manufacturing will be compensated for by inflows or creation of innovation-based manufacturing plants. The pharmaceutical industry is one example of this type of industry.

The European pharmaceutical industry is among the most regulated in the world. Regulation takes the form of strong safety norms with certification processes for drugs, intellectual property rights, and price control mechanisms. Governments justify price regulation as a means to promote equity in access to drugs and reduce costs to national health care systems. Simple theory predicts that price regulation in any particular country might affect the total investment of the pharmaceutical industry, if regulation reduces total expected profits from investment. However, to the extent that the market for pharmaceuticals is a global one, we might not expect to observe any correlation between regulatory regimes and the *location* of investment. And yet it has been suggested that pharmaceutical firms respond to controversial policy choices by "voting with their feet" and avoiding locations with stricter price regulation. A report of the U.S. Trade Representative observes that, "R&D in the United States quadrupled between 1990 and 2003, while R&D in Europe grew by only 2.6 times. One of the factors that may be contributing to this relative decline is the regulatory and competitive environment for pharmaceuticals in Europe" (see U.S. Dept. of Commerce, 2004, p. 34). Most recently, in response to price cuts of up to 23% on patented drugs in Spain, the president of the Spanish pharmaceutical industry association Farmaindustria predicted job losses and said that the cuts "will mean the destruction of the current model of pharmaceutical industry that operates in Spain." (*The Pharmaletter*, May 17 2010, "Spain announces big drug-price cuts, aiming for 1.6 billion savings"). Merck was said to be "re-evaluating" its investment in Brazil after that country

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imposed compulsory licensing on efavirenz, Merck's anti-retroviral AIDS drug. (*The Economist*, May 10 2007, "Brazil's AIDS Program: A conflict of goals"). In response to reform proposals in Germany 2002, the Pharma Marketletter reported that the pharmaceutical company Merck KGaA "warned that the reforms could ... influence where it locates a new 300-million euro biopharmaceuticals product plant, its largest-ever investment." Die Welt reported on August 25, 2003 that "the American pharmaceutical firm Pfizer plans to reduce certain activities in Germany following upcoming reforms to the health system. Pfizer has decided to transfer an R&D group from Freiburg, Germany to the United Kingdom. 150 jobs will be affected by this decision." There is also evidence that drug launches are delayed in countries with more stringent price regulations (Danzon et al., 2004; Kyle, 2006, 2007a).

In this paper, we investigate the determinants of the locations of foreign investments in the biopharmaceutical sector in 27 European countries between 2002 and 2009. We investigate whether variation in policy regimes across countries helps explain variation in the locations of foreign investments in the pharmaceutical sector. We present the first evidence of the impact of regulatory constraints on the location choice of affiliates by multinational pharmaceutical firms. Our empirical results suggest that manufacturing investments are not associated with regulatory policy. Non-manufacturing investments in Western Europe are negatively associated with the strength of price regulation in a given country. However, these findings appear to be driven in large part by a decline in investments related to administrative functions.

The rest of the paper is structured as follows. Section 2 describes the regulatory policy schemes in the pharmaceutical industry in Europe and sketches the theoretical framework. Section 3 presents the empirical strategy to estimate the effect of regulatory policy on the location choices of pharmaceutical firms. In Section 4 we present the investment data, Section 5 explains the results and Section 6 concludes.

2. Regulatory policy and investment in the pharmaceutical industry

We first describe the different policies used by European countries to control the pricing of drugs and reimbursement of expenditures. Then we discuss the theoretical effect of price regulations on the location of pharmaceutical investment.

2.1. Price regulation policies in Europe

The pharmaceutical industry is perhaps the industry most affected by regulatory choices. Policies concerning the duration and strength of exclusivity awarded by patents are particularly important. The latter policies are essentially consistent across European countries (although the pharmaceutical industry has expressed concern over the enforcement of these rights in some countries), as are policies relating to advertising, wholesale distribution, packaging and labeling of drugs. These homogenized policies are by definition not expected to influence the profitability of the different countries. This is however not the case in the medical sector. As discussed at length by Permanand and Mossialos (2005), "Despite the harmonizing imperative of the SEM, there is still no single European market in medicines." European countries retain control over the pricing of drugs and reimbursement of expenditures. Countries vary in the use of reference pricing, fixed pharmacy profit margins, profit controls for manufacturers, as well as along other dimensions (see Table 2 of Kyle (2007a) as well as Jacobzone (2000)). Countries also vary in their attitudes to parallel trade, or the re-importation of drugs from countries in which prices are lower. All EU countries exert some degree of influence over expenditures on drugs marketed within their boundaries, but individual governments employ different policies. Governments may use formularies (lists of drugs for which patients will be reimbursed), controls on doctors' prescribing behavior, pharmacists, reimbursements of prescription costs, and/or price controls. A common mechanism for controlling prices is to set a price not higher than that of a currently available generic substitute, or to set the price with reference to prices of the same drug in neighboring countries. Some countries (like Spain and the UK) place controls on the profits of pharmaceutical companies. Others, like Denmark, do not control the price charged by the manufacturer, but prohibit price increases after a drug is introduced. Many EU countries also regulate the profit margins of pharmacists. Some countries (like Belgium, France, Spain and the UK) also regulate expenditures on drug marketing (Kyle, 2007a).

Our empirical investigation concentrates on the following price regulation policies, which we now define: price controls, reference pricing, and therapeutic reference pricing, in each of which price freezes and price cuts can be introduced. Detailed information on the use of these polices in different countries is available in Tables 1–3.

Price controls refer to policies that directly control the manufacturer's, wholesale, or retail price of pharmaceuticals. The determinants of the price vary from country to country. Countries like Belgium, Spain, France, Hungary, Poland, Latvia, and Lithuania set prices after negotiation with drug companies (Kyle, 2007a; Kanavos, 2002; Mossiolos et al., 2004). Other countries (Bulgaria, Czech Republic, Estonia, Finland, Greece, Hungary, Ireland, Latvia, Lithuania, Norway, Poland, Romania, Slovenia, Sweden) use a weighted average of prices charged for the same drug in selected other countries (Norway substituted reference pricing for a price cap starting in 2003 for a limited number of off-patent drugs (Brekke et al., 2008)). Reference pricing is a practice in which governments set a maximum reimbursement amount for drug purchases with reference to prices of substitute drugs. It is used in Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway,[1] Poland, Portugal, Romania, Slovakia, and Spain (Kyle, 2007a; Mossiolos et al., 2004; Podnar et al., 2007). Danzon and Ketcham (2003) notes that it has typically been used in countries without price controls, and is seen as a less stringent alternative to explicit price controls. However, Danzon notes, "In practice, certain forms of reference pricing can be de facto at least as stringent...particularly for new products." The stringency of reference pricing largely depends on which drugs' prices are used for reference. In some cases, only generic equivalents with the same active ingredient fall into the reference group. In other cases, the reference group consists of any therapeutic substitute on the market, and the drug's prices in other countries are taken into consideration. Most, but not all, countries exempt patented drugs from reference pricing schemes. As Danzon notes, "The decision whether to include on-patent products and to cluster on-patent products with off-patent products raises a critical trade-off between cost control and incentives for R&D, in addition to the issues of therapeutic substitutability." These two forms of price setting for reimbursement will be respectively denoted RP (reference pricing) and TRP (therapeutic reference pricing) in the empirical section of this paper. We define a country as having a reference pricing regime when it sets reimbursement levels for drugs with reference to prices of

[1] Norway uses a step-price system known as "trinnpreiser" for off-patent drugs that clusters at the ATC5 level and resembles a reference price system (PPRI Country Profile, Norway). We follow Kyle (2007a,b), in which this is classified as a RP system for the purposes of data analysis.

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Table 1
Main price regulation variables used in this study.

	Price control	Reference pricing	Therapeutic RP	Number of benchmarking countries in EU
Austria	Yes	No	No	8
Belgium	Yes	No	No	8
Bulgaria	Yes	No	No	3
Czech R.	Yes	Yes	Yes	9
Denmark	No	Yes	No	7
Estonia	Yes	Yes	No	4
Finland	Yes	No	No	4
France	Yes	No	No	14
Germany	No	Yes	Starting in 2004	14
Greece	Yes	No	No	6
Hungary	Yes	Yes	Starting in 2003	9
Ireland	Yes	No	No	7
Italy	Yes	Yes	No	11
Latvia	Yes	Yes	Starting in 2005	5
Lithuania	Yes	Starting in 2003	No	6
Luxembourg	Yes	No	No	6
Netherlands	No	Yes	Yes	8
Norway	Yes	Yes	No	2
Poland	Yes	Yes	Starting in 2005	8
Portugal	Yes	Starting in 2003	No	8
Romania	Yes	Yes	No	4
Slovakia	Yes	Yes	Yes	4
Slovenia	Yes	Starting in 2003	No	5
Spain	Yes	Yes (except 2005–2006)	No	8
Sweden	Yes	Yes	No	7
Switzerland	Yes	No	No	3
UK	No	No	No	10

Source: Austria, Belgium, Czech, Finland, France, Greece, Ireland, Norway, Sweden, Switzerland, UK: Kyle and Jacobzone. UK, Italy: Kyle, Jacobzone and Huttin. Spain and Hungary: Kyle, Jacobzone, and Kalo et al. Denmark and Germany: Kyle, Jacobzone, Puig and Kaiser. Poland, Slovenia, Bulgaria: PhRMA. Slovakia and Lithuania: USITC. Estonia, Latvia, Romania: WHO. Luxemburg: Huttin. Portugal: Huttin and Mossiolos. "Number of benchmarking countries" refers to the number of other European countries that reference the listed country's drug prices when setting the price of drugs in the home market. Source of information on countries included in benchmark lists: OECD (2008), p. 103, and PPRI.

substitute drugs or the same drug in other markets. Most reference pricing systems make price comparisons at the level of the active ingredient (or level 5 of the Anatomical Therapeutic Chemical (ATC) Classification system used by the World Health Organization). By contrast, we call a country's system a therapeutic reference pricing regime when the price comparisons are made between drugs that are in the same therapeutic class but have different molecular structures (e.g., level 4 of the ATC system or broader).

Germany established its reference pricing system in 1989. The comparison group for some products was drugs with the same active ingredient, but for others the comparison group included chemically distinct products with similar therapeutic effects. As of 2000, roughly half of drug expenditures were covered by the reference pricing system.[2] Germany exempted patented drugs from the reference pricing scheme in 1996. However, in 2004 this exemption was removed, causing the sales of a number of on-patent drugs to fall dramatically. This policy shift was preceded in 2003 by a 16% reduction in reimbursed prices on patented medicines. Poland and Latvia instituted TRP regimes in 2005 (Adamski et al., 2008; Puig-Junoy, 2010). Hungary introduced a limited TRP regime in 2003 (Kalo et al., 2007; Sood et al., 2008, p. 131) and expanded it to

Table 2
Price cuts and freezes, 2002–2009.

Country	Date	Description
Germany	October 2002 to December 2004	Manufacturers must submit revenue from price increases to government.
Germany	October 2003	16% reduction in reimbursed prices for patented medicines.
Hungary	2004	15% price cut April–June.
UK	2005	7% cut in branded drug prices.
Spain	2005–2006	Compulsory 4.2% price cut from March 2005 and a 2% price cut from March 2006 for all products not subject to reference prices and with a price higher than EUR 2.
Germany	November 2005 to March 2008	Manufacturers must submit revenue from price increases to government.
Italy	2006	Temporary 5% cut on the price of drugs used by the country's National Health Service.
Poland	2006	13% price cut for imported products.
Finland	2006	5% cut of approved wholesale prices.
Ireland	2006	Wholesale prices frozen.
Denmark	2007–2008	Price ceilings imposed.
UK	2009	5% price cut.

Source: PPRI Country Profiles.

Table 3
Changes to reference pricing programs.

Country	Date	Description
Portugal	2003	Begins reference pricing
Hungary	2003	Begins therapeutic reference pricing
Lithuania	2003	Begins reference pricing
Slovenia	2003	Begins reference pricing
Spain	2004	Expansion of reference price regime to include more products; mandatory prescription of lowest-price generic
Germany	2004	Patented drugs included in therapeutic reference pricing scheme.
Denmark	2005	Reference price changed from average of other European countries to lowest domestic price in reference group.
Poland	2005	Begins therapeutic reference pricing
Latvia	2005	Begins therapeutic reference pricing
Greece	2005	Begins reference pricing

Source: Vogler et al. (2009), Kaiser (2010), Puig-Junoy (2007).

[2] Danzon et al. (2004), p. 7.

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50 additional therapeutic groups representing over a third of the prescription market in 2005.[3]

Two additional reforms to countries' reference pricing regimes that took place over the course of our sample period are relevant to our study. Both cases constitute changes to the RP regime that effectively shifted the comparison group to lower-priced drugs. Up to 2005, Denmark set the reference price of a drug as the European average price for drugs with the same active ingredient (ATC5). In 2005, the reference price became the minimum price in Denmark alone for drugs with the same active ingredient. Kaiser et al. (2010) show that this change led to a substantial decline in prices, with list prices declining by 27% on average and reference prices falling by 33%.[4] Spain also "radically modified" (Vogler et al., 2009, p. 221) its reference pricing system in 2004 and 2006. Spain's reference pricing system, established in 2000, calculated reference prices for products for which a bio-equivalent generic was available. The reference price was based on the weighted average of the lowest-priced substitutes with a combined market share of at least 20%. Patients would be reimbursed up to the reference price, but could opt to buy drugs at higher prices and pay the difference out of pocket.[5] As of 2004, however, the reference price was calculated as the average of the three lowest costs per treatment per day for the products in the group, for each form of administration.[6] In cases in which the price of a prescribed drug is above the reference price and there is a generic in the reference group, pharmacists are required to dispense the cheapest generic in the reference group.[7] Also, the prices of generics that are above the reference price in the reference group must be reduced to at most the reference price. Vogler et al. (2009) note that these reforms to the Spanish system gradually expanded the share of the market covered by reference pricing to roughly half the market by 2008. One reason why this change was significant is that in Spain, in contrast to other European countries, customers no longer had the option of paying the difference between the reference price and a pharmacy retail price. Thus, the price impacts of the aforementioned reforms are likely to be particularly large.[8]

In the analysis that follows, we consider the impacts of these changes to reference pricing regimes that took place during our sample period. We create a "policy change" dummy variable that indicates that a government undertook a major change to the reference pricing system aimed at reducing prices. The policy changes we include in this category are (1) the shifts from RP to TRP that took place in Germany, Hungary, Latvia and Poland, and (2) the major changes to the RP systems that took place in Denmark and Spain.[9] The dummy variable is equal to zero in the years before the change and one afterwards. We also include a "price freeze" dummy, equal to 1 in countries and years in which there was a price freeze or cut in effect, and 0 otherwise. The relevant freezes and cuts are listed in Table 2.

Changes like those that took place in Germany are a key element of this study. Most countries do not change their regulatory policies during the time frame of our sample. For example, all of the countries with explicit price controls in our sample maintain these controls throughout the time frame. As a result, it may be difficult to separate the effects of these invariant policy choices from unobserved, invariant characteristics of the country. However, countries that change their policies during the sample period provide an opportunity to examine investment patterns before and after the change. The change in Germany's reference pricing scheme is one such opportunity. Other changes to reference pricing schemes during our period took place in Denmark, Hungary, Latvia, Spain, and Portugal. Additional variation in the drug price policy environment can be obtained from price freezes and cuts that were instituted in several countries during our period. Table 1 contains information on the use of these policies in different countries and Tables 2 and 3 list all the policy changes relevant to this paper.[10]

2.2. The effect of price regulations on the location of investment

We will test the hypothesis that these differences in regulations across countries have side-effects on the location of investments. Our FDI dataset includes investments in manufacturing plants, R&D facilities, and other investments related to administrative or sales functions of the firm. In most industries, the location of manufacturing investments is mainly driven by considerations of cost and demand. Firms may locate manufacturing investments near large markets in order to minimize the cost of transporting finished products to those markets. Alternatively, if transport costs are low, firms may prefer to locate in the lowest-cost region, and location will be dictated more by tax rates and production costs than by proximity to demand. The pharmaceutical industry is characterized by large sunk development costs, low transport costs, and a strong link between government regulation and profitability. As stated by the OECD, "the market for pharmaceutical products is increasingly a global one (...). New active ingredients are launched in an average of ten countries, although manufacturers often release multiple versions of their on-patent products in different markets to reflect consumer preferences and to reduce opportunities both for prospective buyers to make external price comparisons and for wholesalers to engage in parallel trade" (OECD, 2008, p. 11). While price regulation clearly affects the overall level of anticipated profits and therefore the overall level of investment, the location of production may not be tied as closely to the location of demand as for some other products that have higher transport costs or that are customized to particular markets. Conditional on the size of the market in terms of income, we might therefore not expect to see more pharmaceutical production in countries with higher prices if those countries also have high production costs.

We expect that the location of R&D investments will typically be loosely linked to the location of demand. This is because R&D produces ideas which can be costlessly transferred to the location of production. R&D location decisions will then be influenced more by the cost of employing skilled researchers than by any consideration of the location of demand, and we will tend to see R&D located in

[3] "Hungary widens Rx reference pricing", *The PharmaLetter*, July 4, 2005.
[4] Kaiser et al. (2010), p. 3.
[5] Moreno-Torres et al. (2007), p. 5.
[6] Vogler et al. (2009), p. 222.
[7] Puig-Junoy (2007).
[8] Vogler et al. (2009), p. 222.
[9] Slovenia introduced reference pricing (at the ATC5 level) in 2003, and Greece did the same in 2005. Because reference pricing is generally considered to be a softer form of regulation than price controls or TRP, we do not include these changes in our "policy shift" variable, which is intended to capture increases in the stringency of regulation. However, because there are so few investments in these countries, including or excluding their changes in policy has very little impact on the results. Limited therapeutic reference pricing was also initiated in 2006 in the Italian regions of Puglia and Abruzzo for Proton Pump Inhibitors and in Liguria for PPIs, statins, SSRIs and treatments for benign prostatic hypertrophy. However, a law passed in 2008 ruled out further changes to the reference pricing scheme by the regions (CRA Insights). Because these changes affected only a small share of the Italian pharmaceutical market, we do not classify Italy as having therapeutic reference pricing in our analysis.
[10] An increasingly important and controversial factor in the pricing of drugs in the EU is parallel trade, or the re-export of drugs from low-price countries (like Spain, Portugal and Greece). While parallel trade has the potential to lead to price compression within the EU (and has been found to do so in non-drug markets), Kyle (2007b) shows that in fact parallel trade has had little impact on drug prices, due in part to strategic responses by pharmaceutical companies.

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countries with high concentrations of workers with advanced scientific training.[11] As an alternative to the purely global view of the industry, Fabrizio and Thomas (forthcoming) find that patenting by firms in particular therapeutic classes is positively associated with demand for that type of drug in the firms' home countries.

And yet, as evidenced by some of the quotes in the introduction, some pharmaceutical firms threaten to restrict investment in countries with strict regulation. Is this just cheap talk? Or do pharmaceutical firms actually shift the location of investment in response to the imposition of stricter price controls by governments?

The theory of "private firms subject to political influence," of Shleifer and Vishny (1994) provides one illustration of why firms might reduce investment in countries that tighten price regulation. While Shleifer and Vishny's model is motivated largely by a desire to understand the behavior of publicly controlled firms, the authors observe that "Many private firms in Europe and the United States get subsidies and tax breaks in exchange for hiring more people, or locating in particular areas." One can consider an increase in the strictness of price regulation as the weakening of a type of subsidy to pharmaceutical firms.

In this model, a politician and a manager bargain over L, excess employment by the firm (workers hired above the profit-maximizing level) in exchange for transfers from the government, T. The politician earns a political benefit from employing people B(L), and incurs a political cost of giving the firm a subsidy C(T). In our case, we think of the subsidy T as the difference in revenues the firm earns relative to some counterfactual level of profits in a more rigid price control regime. The politician and the manager bargain over L and T. The politician controls T, but either the firm or the politician can be assumed to control L. In cases in which politicians have strong bargaining power vis-a-vis firms, we can think of the politician choosing L to maximize his utility.

Consider the example of Germany in 2004, where the stringency of regulation increased and investment in R&D fell. With a decreasing marginal benefit of employment and an increasing marginal cost of the transfer, if the marginal political cost of the subsidy increases for the politician (perhaps in response to a shift in voters' tastes for drug price regulation), the increase in the marginal cost of the transfer would generate an inward shift in the set of optimal combinations of L and T. This will result in a reduction in the subsidy to firms accompanied by a reduction in investment that is the focus of our empirical analysis.

As one of the largest markets in Europe, actions taken by Germany may affect other markets in two ways. Many countries use external price benchmarking – the calculation of an average price of a drug in certain other countries – to guide the setting of price or reimbursement limits. Prices for drugs charged in Germany factor into other countries' pricing or reimbursement decisions in 14 other EU countries. As a result, lower prices in Germany lead to lower prices elsewhere. The median number of referencing countries in our sample is 7.[12] Moreover, Germany's policy changes may have been viewed by the pharmaceutical industry and other regulators as a test case - if the industry did not react strongly to the change, such changes may have appeared more attractive in other countries. Germany was the first country to establish reference pricing in 1989, followed by the Netherlands and Hungary (1991), Sweden, Denmark and New Zealand (1993), and 14 other European countries in later years.[13] Pharma Marketletter quoted a Merrill Lynch analyst who pointed out the potential snowball effects of Germany's shift to TRP, asking, "what's to stop France and Italy following guidance from Germany?"[14].

Softer price regulation in very influential countries like Germany thus generates much larger subsidies for firms because of the follow-on effects of their policies in other countries. Meanwhile, other less influential countries would have to reduce prices much more to generate the same implicit subsidy to firms. This is one reason why the equilibrium level of investment in less-influential countries will be lower. We test this prediction of the model by examining differences in the response of firms to price regulation in different countries, according to how that market's regulatory decisions affect prices elsewhere (see Table 8).

An alternative mechanism through which price regulation could also affect investment is through its effects on incentives for stimulating demand. It is worth noting that the non-manufacturing, non-R&D investments in our sample include sales offices (classified as *bureau commercial ou de liaison*), distribution or logistics centers, and offices providing administrative support. Some of these investments will resemble R&D facilities in that they are performing administrative functions that are not necessarily linked to the location of demand. Other types of non-manufacturing, non-R&D investment, specifically those engaged in marketing functions, may be more likely made in markets with growing demand or with less stringent price regulation, because investments in influencing consumers' preferences may have a higher return. We might expect these investments to decline after changes in the regulatory regime if marketing efforts are less profitable when prices are more tightly controlled. We will investigate this possibility in the empirical section.

The existing literature highlights the influence of regulatory policies on the decision-making of pharmaceutical firms in terms of product launch, or pharmaceutical employment. Kyle (2007a), in a detailed analysis of international drug launch strategies, shows that drug launches are delayed in countries with price controls. With a focus on developing countries, Lanjouw (2005) shows that drugs are launched earlier in countries with stronger enforcement of Intellectual Property Rights (IPRs). On the other side, Ahlering (2004), in a study of the relationship between regulatory and policy variables in a particular country and the share of a pharmaceutical company's employment in that country, finds little relationship between employment in a country and such factors as intellectual property protection (using the Ginarte-Park index to measure the strength of IP), drug approval times, corporate tax rates, and R&D incentives. Ahlering finds evidence of a positive relationship between the number of price control mechanisms in a country and the share of a company's employment in that country.

It is worth noting here that our analysis focuses on the official regulatory policies in place in our sample countries, rather than the actual price level. It is possible that policies may not be effectively enforced, or softened by other interventions with the net result of no significant reduction in prices relative to other markets. If this is the case, there may not be a significant link between announced policies and investment choices. Revisiting the literature on price regulation and launch decisions, and measuring prices directly, Danzon and Epstein (2008) show that price regulation does deter product launches in markets in which regulation succeeds at reducing prices.

[11] For example, Furman et al. (2006) show that pharmaceutical patents in a particular therapeutic class and location are positively associated with the number of related scientific articles in that location.

[12] *Source*: OECD (2008) and PPRI (2007). We were unable to determine which (if any) countries were used for price comparisons in Romania.

[13] Vogel et al. (2009).

[14] "Govt drug price controls continue to threaten Europe's pharma industry", Pharma Marketletter, December 23, 2002.

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The following section develops our empirical strategy to test whether pharmaceutical companies are deterred to locate new investments in countries with more stringent price regulations.

3. The empirical strategy

The literature on the choice of location for FDI has focused largely on the influences of proximity to demand, production costs, taxes and subsidies, and potential spillovers. Our empirical approach builds upon this framework, while recognizing that the location of pharmaceutical investment may also be affected by strategic considerations relating to price regulation.

Carlton and Dennis (1983) was the first paper to use a discrete choice model to study choice of production sites by firms. The subsequent literature analyzed location choices of FDI with the traditional elements of the expected profit in each location, some studies however including a more complete form of demand with the income of contiguous locations (Head et al., 1999), as well as the location of competitors (Head and Mayer, 2004).

A set of contributions have investigated the influence of public policies on the decision to locate in different countries. Head et al. (1999) study the influence of US states' incentives on the decisions of Japanese affiliates to locate within the United States. Crozet et al. (2004) analyze whether regional policies have an effect on location patterns within France, while Devereux et al. (2007) apply similar methods to the English case. Those papers end up with mixed evidence of the impact of public policies. In this paper, we enrich the location choice model to incorporate a role for regulatory policy.

We consider a pharmaceutical firm located in country r. Our estimated equation is a reduced form of the profit of the firm which sells in r and exports to all other markets. This aggregate profit is a decreasing function of the costs of production in r and an increasing function of aggregate demand. We specify the cost as a function of local wages w_r (specified here as the unit labor cost of production at the country level) and add the local statutory tax rate tax_r, which is also likely to affect location decisions as a determinant of the labor market situation. In order to take into account the bilateral cost of investment, we add two variables to the estimation, measuring distance between the investing and the potential host country ($Dist_{ir}$), and whether these countries share a common language ($Lang_{ir}$).

Governmental regulations of the pharmaceutical market enter the estimated equation through PR_r, a matrix of dummy variables capturing various price regulations. These dummy variables indicate whether the country (1) controls prices explicitly, (2) employs reference pricing schemes to control the amounts reimbursed, (3) uses therapeutic reference pricing, (4) made a significant change to the pricing regime or (5) has frozen or cut the prices of drugs at a given point in time. We can think of countries with stricter price regulation as offering lower subsidies – and therefore lower profits – associated with locating in the country. Our regressions will test the hypothesis that these implicit subsidies matter for firms' location decisions.

Proximity to demand may also be a factor. In most industries, this is a key determinant of location choice and as a result the trade and investment literature has focused on the role of market potential (see Head and Mayer, 2004). In the pharmaceutical sector, where transport costs are low and products are relatively standardized across markets, this factor may be less important. Nevertheless, some customization to particular markets does occur, among other reasons to prevent parallel trade (see Kyle, 2007b). Furthermore, countries may be most likely to impose tighten price regulation when spending on pharmaceuticals is growing, and this may also be associated with incentives for investment. As a result, it is important to control for demand in the destination country. To measure the potential demand a firm can expect to face when located in a particular country, we follow Head and Mayer (2004) who used the Krugman market potential M_r. The Krugman market potential applied to the pharmaceutical sector in country r sums the pharmaceutical consumption in all countries importing from r (including r). This sum is weighted by transaction costs between country r and destination countries j, and by an index measuring the degree of competition in each market. The demand addressed to a pharmaceutical firm planning to locate in r is thus increasing with consumption in all importing markets including r. This consumption is, however, reduced by two items: (1) the number of other pharmaceutical firms in each market, and (2) the level of transaction costs between r and each market.[15] The market potential variable is constructed from the estimation of bilateral international trade flows, using the Redding and Venables (2004) method explained in Section 4.

Next, we consider the clustering of research-intensive firms in the same location. We include an agglomeration effect variable, computed as the number of pharmaceutical investments in country r in year t. We hence assume that, controlling for the market potential in country r, and controlling for the competition effect emanating from the presence of competitors in the same industry in country r, the presence of other related firms may be beneficial to a firm considering choosing r. The positive effect may arise from technological spillovers decreasing the input cost c_r, or decreasing the transaction cost τ_{rj}. Furman et al. (2007) (among others) have documented the tendency of biopharmaceutical firms to locate in places with greater R&D capabilities, and as a result we also include the country's annual R&D spending in the pharmaceutical sector. We denote these spillover-related variables $Spill_r$.

The location choice literature typically specifies the profit of a firm located in region i in r as being decomposed into the part observed by the researcher, V_{ir} and the unobserved aspects of the profit e_{ir}. The unobserved elements refer for example to bilateral factors between the firm and the host country affecting the productivity or the firm's production cost. The form of the observed part is specified as the vector of parameters β that we will estimate:

$$V_{ir} = \beta_0 + \beta_1 \ln w_r + \beta_2 \ln tax_r + \beta_3 Dist_{ir} + \beta_4 Lang_{ir} + \beta_5 \ln M_r + \beta_6' PR_r + \beta_7' Spill_r. \quad (1)$$

We assume that firms choose the location yielding the highest profit. With error terms distributed according to an extreme value distribution, the probability that a firm located in i chooses to invest in country r is expressed in the following logit form:

$$P_{ir} = \frac{\exp(V_{ir})}{\sum_j \exp(V_{ij})} \quad (2)$$

We thus estimate the determinants of location choices in the pharmaceutical industry using a logit model, on the data that are described in the next section. Following several papers in the location choice literature (among many others, Coughlin et al., 1991; Head et al., 1999; Guimaraes et al., 2000; Head and Mayer, 2004), we estimate a Conditional Logit model of location choices. This model is particularly well suited to applications in which choices are made based on the observable characteristics of the alternatives. In this case, we model profits as a function of the choice attributes described above and a common set of parameters. Chung

[15] This expression appears as the most rigorous measure of demand used in trade and geography models and can be compared to the original Harris (1954) form of market potential, in which trade costs are set equal to the inverse measure of distance and where the competition index is absent.

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and Alcacer (2002) use the Random Parameters Logit model, which allows the effect of location characteristics to vary across investors. While we do not pursue this estimation strategy, we do examine whether different types of investment respond differently to regulation in some specifications.

Because neighboring countries are economically linked, shocks are likely to be correlated across countries belonging to the same local economy. There may be substitution effects, whereby a change in price regulation in Germany leads to a reduction in investment in Germany and an increase in France, as firms choose a nearby alternative location (there may also be income effects if a reduction in prices in Germany reduces global profits for firms, leading to less investment across all countries). We allow for correlation across geographically proximate countries, using standard errors adjusted for spatial correlation in a manner based on Conley (1999) and Rappaport and Sachs (2003). We account for spatial correlation by applying a weighting function g_{ij} to the estimated variance–covariance matrix of the parameters. The estimator solves $\sum_t \sum_i S_{it}(\hat{\theta}) = 0$, where $S_{it}(\theta) = \delta \log L_{it}(y_{it}, \theta)/\delta\theta$, the vector of derivatives of the log-likelihood for observation *it*. The standard error formula takes the form $Var(\hat{\theta}) \approx (H)^{-1}[\sum_i \sum_t \sum_j \sum_k S_{it}(\hat{\theta}) S'_{jk}(\hat{\theta}) g_{ij}](H)^{-1}$, where H is the matrix of second derivatives of the likelihood function, $H = \delta S'_{it}(\theta)/\delta\theta$, and $g_{ij} = (1 - (distance_{ij}/1000)^2)$ if $distance_{ij} < 1000$ km, and 0 if $distance_{ij} > 1000$ km. We compute the distance between countries as the distance between capital cities.[16]

4. Data

We estimate a model of location choice on 527 investments in the biopharmaceutical sector in 27 European countries during 2002–2009.

4.1. Investment data

The data on inward FDI comes from the Agence française des investissements internationaux (AFII, France's agency for international investments). The database is the result of a comprehensive search by web-crawlers of public announcements of new investments from a variety of sources, including press releases, newspapers and the trade press, and Lexis–Nexis. We originally obtained a dataset containing announcements of foreign investments in all sectors, in Europe, between 2002 and 2006. We later obtained access to updated data for 2007–2009, but only for the biopharmaceutical industry. The total number of announcements between 2002 and 2006 is 13,903, among which 672 investments in *biotechnology* and *drugs and cosmetics*, which are the two industry classifications we focus on. Between 2007 and 2009 there are 437 investments in pharmaceuticals and biotechnology. The AFII dataset contains information on the date of the announcement, the location of the investment (country, and sometimes city), the activity undertaken (R&D, manufacturing, distribution, administrative, etc.), the identity and country of origin of the investor, and the projected number of jobs created (in some but not all cases).

While the AFII database contains information on both new investments and expansion of existing investments, we restrict our attention to investments which represent the creation of a new facility. Investing firms may be producers of branded drugs, generic producers, medical services manufacturers, contract research organizations, and suppliers of intermediate inputs. These firms were identified by reading the text of the investment announcement, which typically contained a description of the firm's main activity, and by looking up companies on the web. Among these we focus on producers of branded drugs and analyze the behavior of generic producers separately. Our hypothesis is that only investments by research-driven pharmaceutical firms may be negatively affected by the regulatory regime, since it is primarily the profit margins of these firms that are affected by price regulation. We therefore focus on research-driven firms in our main analysis. We include results restricted to generic firms in a separate table as a robustness check. Finally, investments vary by the main activity. Out of a total of 527 investments, there are 205 announcements of new investments in sales offices or distribution facilities, 121 manufacturing plants, 124 new R&D facilities, 59 headquarters and administrative offices, and 18 other types of announcements (distribution centers, call centers, etc.).

The origin countries of investing firms are in all parts of the world. Destination countries are the current EU members, minus Malta and Cyprus and plus Norway, Switzerland, so in total 27 countries. Table 4 and Fig. 1 summarize the number of investments by country. The United Kingdom, Germany and Ireland are the three countries receiving the largest number of biopharmaceutical investments over the period. These three countries receive a relatively stable number of investments each year, whereas Spain for example exhibits a decreasing trend, and Switzerland displays an increase in investment, particularly toward the end of the period. The Baltic countries, Norway and Luxembourg saw the least amount of investment during 2002–2009.

Table 5 displays the number of investments as a percentage of all investments in our sample countries for countries that increased the stringency of pricing regimes during the period. While the absolute number of investments may have increased in some cases, the table shows that all of these countries experienced a relative decline in investment when compared with other potential destinations after the change in policy (with the exception of Latvia, which went from 0% of European investments to 0.5%). This provides preliminary support for the hypothesis that firms re-directed investment away from countries that tightened price regulation during the sample period.

4.2. Explanatory variables

Our explanatory variables include the traditional FDI determinants and our main variable of interest, drug price regulations. Information on regulatory policies mainly comes from Kyle (2007a), and was supplemented with data on a larger set of European countries and a later time period using the sources described in Appendix A.

Price regulations are in the form of three dummy variables indicating whether each country uses each price policy: price control, reference pricing and therapeutic reference pricing. Table 1 and Fig. 2 summarize this information. We use two additional variables explaining which countries have experienced changes in their regulatory framework during the 2002–2009 period. These are displayed in Tables 2 and 3.

The remaining explanatory variables refer to the traditional determinants of FDI used in the location choice literature. Following Eq. (1), we start with variables relative to local production costs: unit labor costs come from the Structural Business Statistics database from Eurostat's Industry, Trade and Services division. Eurostat's data are available through 2007. We

[16] To incorporate spatially correlated errors in the Conditional Logit model, we modified code originally written by Conley and posted at the following website http://faculty.chicagobooth.edu/timothy.conley/research/gmmcode/statacode.html. This code uses a Cartesian distance measure based on the distance between coordinate points. We calculate distances using the distance between degrees of longitude at the 45th parallel (81 km), which is approximately the median latitude in our dataset.

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Table 4
Bio-Pharmaceutical FDI by country and year.

	Country	2002	2003	2004	2005	2006	2007	2008	2009	Average
AUT	Austria	1	2	0	4	0	1	0	1	1.125
BEL	Belgium	1	2	6	4	1	7	6	3	3.750
BGR	Bulgaria	0	0	1	0	4	0	1	0	0.750
CHE	Switzerland	0	1	3	5	2	10	10	1	4.000
CZE	Czech Republic	1	0	1	1	1	2	2	1	1.125
DEU	Germany	7	6	4	6	11	9	11	3	7.125
DNK	Denmark	3	6	3	2	3	4	0	2	2.875
ESP	Spain	12	8	2	3	1	4	6	4	5.000
EST	Estonia	0	0	2	0	1	0	0	0	0.375
FI	Finland	0	1	1	1	0	1	0	1	0.625
FRA	France	5	1	3	7	2	2	9	8	4.625
GBR	United Kingdom	7	6	11	14	12	20	20	2	11.50
GRC	Greece	0	1	0	2	0	2	0	0	0.625
HU	Hungary	3	2	1	3	1	3	4	1	2.250
IRL	Ireland	6	5	8	7	5	2	5	3	5.125
ITA	Italy	1	0	2	2	3	7	7	1	2.875
LTU	Lithuania	0	0	0	0	1	0	1	1	0.375
LUX	Luxembourg	0	0	0	1	0	1	0	1	0.375
LVA	Latvia	0	0	0	0	1	0	1	0	0.250
NLD	Netherlands	0	1	1	2	3	5	5	2	2.375
NOR	Norway	0	0	0	0	0	0	1	1	0.250
POL	Poland	1	2	4	3	1	2	2	2	2.125
PRT	Portugal	1	0	0	3	1	2	3	2	1.500
ROM	Romania	1	0	0	0	0	1	4	1	0.875
SVK	Slovakia	0	0	0	0	1	1	0	0	0.250
SVN	Slovenia	0	0	2	0	1	1	0	0	0.500
SWE	Sweden	3	3	5	5	0	2	3	5	3.25
Mean		1.963	1.741	2.222	2.778	2.074	3.296	3.741	1.704	

Source: AFII database.

Fig. 1. Bio-pharmaceutical FDI in Europe, 2002–2009.

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Table 5
Investments in EU countries reforming pricing regimes during sample period.

Year	Total	DEU	DEU, % of total	DNK	DNK, % of total	HUN	HUN, % of total
2002	53	7	13%	3	6%	3	6%
2003	47	6	13%	6	13%	2	4%
2004	60	4	7%	3	5%	1	2%
2005	75	6	8%	2	3%	3	4%
2006	56	11	20%	3	5%	1	2%
2007	89	9	10%	4	4%	3	3%
2008	101	11	11%	0	0%	4	4%
2009	46	3	7%	2	4%	1	2%
Pre-reform			13%		8%		6%
Post-reform			10%		3%		3%

Year	POL	POL, % of total	ESP	ESP, % of total	LVA	LVA, % of total
2002	1	2%	12	22%	0	0%
2003	2	4%	8	17%	0	0%
2004	4	7%	2	3%	0	0%
2005	3	4%	3	4%	0	0%
2006	1	2%	1	2%	1	2%
2007	2	2%	4	4%	0	0%
2008	2	2%	6	6%	1	1%
2009	2	4%	4	9%	0	0%
Pre-reform		4%		19%		0%
Post-reform		3%		5%		0.50%

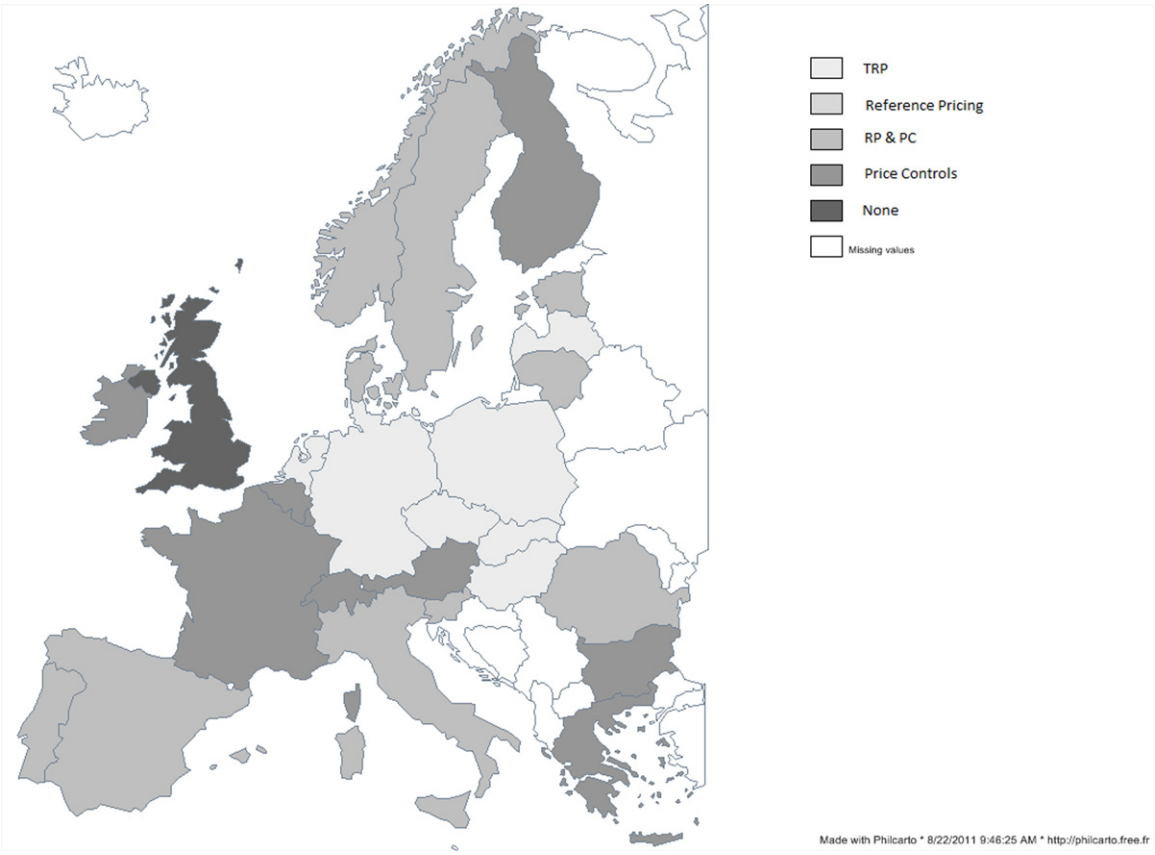

Fig. 2. Price regulations in Europe as of 2009.

extrapolate each variable forward to 2009 from 2001 to 2007 data.

Data on corporate taxes come from three sources. The first is the Devereux et al., 2002Devereux, Griffith and Klemm (2002) database, available from the IFS. This dataset omits information for the new EU members and stops in 2005. We fill in information on statutory tax rates in new EU members in 2003 and 2004 from Finkenzeller and Spengel (2004). We supplement this data with information from KPMG's Corporate Tax Rate Surveys 2006–2009. Data accounting for spillovers (R&D spending and the number of firms in the pharmaceutical sector for each country) are also extracted from the Eurostat database.

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The construction of a market potential variable requires data on three elements: trade costs between countries r and j, consumption in pharmaceuticals in country j, and the competition index in j. Following Redding and Venables (2004), we obtain these terms by estimating gravitational trade equations. Bilateral exports from r to j, X_{rj}, can be written as the amount exported by a representative firm from r, $p_{rj}q_{rj}$, multiplied by the number of firms in r:

$$X_{rj} = n_r p_{rj} q_{rj} = n_r c_r^{1-\sigma} \tau_{rj}^{1-\sigma} \frac{Y_j}{G_j}.$$

In logs, the latter equation writes: $\ln X_{rj} = \ln(n_r c_r^{1-\sigma}) + \ln \phi_{rj} + \ln(Y_j/G_j)$. $\phi_{rj} = \tau_{rj}^{1-\sigma}$ represents the freeness of trade between the two countries, and is specified as depending on distance, borders and language as follows: $\phi_{rj} = d_{rj}^{-\delta} e^{[-(\beta_j - \lambda L_{rj})B_{rj} + \epsilon_{rj}]}$. d_{rj} is distance between r and j, L_{rj} and B_{rj} two dummy variables taking the value 1 if countries r and j respectively share a common language or share a common border. ϵ_{rj} is an error term and β_j and λ are two parameters to estimate.

We use bilateral trade data for the years 2002–2009 in the pharmaceutical industry, and following Redding and Venables (2004) we estimate the trade equation with fixed effects for the exporting and the importing countries, respectively FX_r and FM_j. This estimation allows to obtain a dummy per importing country, and coefficients on distance, common border and common language, with which we can build the trade costs variable. The next step is to construct the market potential variable for each country using trade costs and the importers' fixed effects: $M_r = \sum_j \phi_{rj} Y_j / G_j$. Data on common languages and on distance between countries come from CEPII, a French research center in International Economics. Trade data come from Eurostat's structural indicators and are available online. Fig. 3 displays the differences in market potential across European countries, reflecting for instance the importance of Belgium as a central market, due to vicinity to large centers of demand.

5. Empirical results

We first present the results obtained from the cross-sectional price regulation dummy variables in Tables 6 and 7, and then turn to the results on the time-varying regulatory variables (Table 8).

5.1. Cross-sectional results

The first column of Table 6 includes only the set of explanatory variables related to price regulation. These unconditional estimates show that overall, countries with price controls (PC) are less likely to be chosen as a destination for investment than countries without price controls. Countries with reference pricing (RP) and countries with therapeutic reference pricing (TRP) are also less likely to receive investment, but the effect is not as strong as for price controls and is not statistically significant for TRP. And countries that combine all three systems (price controls, reference pricing, and therapeutic reference pricing) see the least investment.

However, this regression omits important confounders, and in column 2, we add the market potential variable, which is positively and significantly related to the location of FDI.[17] In column 3 we add variables relating to trade costs. These are a dummy for a common language between investors and potential recipient countries, the distance between countries, and a dummy variable for Eastern European destinations. The first and third of these are highly significant, though the price control dummy retains its negative and significant association with the probability of investment. We continue to add the elements of the profit function in columns 4 and 5. As expected, the log of the nominal corporate tax rate is negatively associated with investment (though it is only statistically significant for manufacturing investments), while the unit cost of production has a positive coefficient (presumably reflecting variation in productivity or labor quality across locations). The latter finding is consistent with Head and Mayer (2004).[18]

When the "spillovers" variables are included in column 6, the market potential variable becomes insignificant, reflecting the high positive correlation between these variables. The coefficient on the price control dummy increases from −0.514 to −0.251, but remains significant at the 1% level. We separate manufacturing and non-manufacturing investments in columns 7 and 8, 9, and find that the association between regulation and investment appears to be driven by non-manufacturing investments as the regulatory coefficients are insignificant in the specification restricted to manufacturing. Column 9 includes the log of the number of non-pharmaceutical investments in the AFII database by country and year,[19] which controls for other, non-pharmaceutical related motives for investment. There is no significant correlation between pricing policy and manufacturing investment, but columns 8 and 9 show that countries with price controls see fewer non-manufacturing investments than those without, even after controlling for the amount of non-pharmaceutical FDI in the country.

The inclusion of the spillover variables is somewhat problematic. While the theory suggests an important role for inter-firm spillovers, the variable with which we measure spillovers (the number of pharmaceutical establishments in the country) makes it difficult to separately identify spillovers from other motives for investment. If the regulatory regime affects the location choices of firms, this will influence the number of establishments that previously located in the country. Thus, by controlling for the *existing* number of establishments, we are picking up the effect of the regulatory regime on the *change* in the number of establishments in the country. As a result, our preferred specifications for interpreting the effects of the time-invariant regulatory variables on investment will be those that exclude the spillovers variables. We will then turn to an analysis of time-varying regulatory variables with country fixed effects, exploiting policy changes during our sample period to identify the effects of an increase in regulatory stringency on changes in investment choices.

Given that investment patterns may differ substantially between Western European countries and locations in Eastern Europe and the Baltic states, we present models estimated separately for these two regions in Table 7. Regulation has no negative effect on location decisions in Eastern Europe (in fact, the coefficient on RP is positive). It is somewhat difficult to interpret the results restricted to Eastern Europe because all countries in Eastern Europe use price controls, so we cannot estimate the effect of price controls within this region. The effect of reference pricing is also

[17] We do not have information on bilateral trade in pharmaceuticals for Norway, and as a result this country is omitted from subsequent regressions. Results are similar when imputed data is used and Norway is retained.

[18] The number of observations falls in column 4 due to missing data on costs in Switzerland, Estonia, Greece and Luxembourg. These countries have little influence on the results due to the relatively small number of investments that take place there during this period (32 in Switzerland, 3 in Estonia, 5 in Greece, and 3 in Luxembourg).

[19] We only have the full dataset until the end of 2006. We extrapolated data for 2007–2009 using OECD FDI data (we regressed the number of non-pharma investments on the total dollar amount of FDI investment, computed fitted values, and filled in the missing data with the fitted values). Where OECD data were not available, we used linear projections based on the trend in the number of investments during 2002–2006.

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Table 6
Baseline results including all countries, types of investments, investors.

	Dependent variable: location choice dummy								
	Estimation method: conditional logit								
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Full sample						Manufacturing	Non-manufacturing	
Price regulation	−1.309***	−0.444***	−0.363***	−0.336***	−0.514***	−0.251***	0.036	−0.438***	−0.591***
	(0.155)	(0.070)	(0.067)	(0.126)	(0.093)	(0.091)	(0.158)	(0.151)	(0.132)
Reference pricing	−0.547***	−0.485**	−0.16	−0.056	0.348***	0.248**	0.107	−0.081	0.353**
	(0.234)	(0.204)	(0.204)	(0.246)	(0.089)	(0.110)	(0.387)	(0.208)	(0.129)
Therapeutic RP	−0.304	−0.355***	−0.125	−0.079	−0.195	−0.238**	0.214	−0.176	−0.292**
	(0.381)	(0.160)	(0.143)	(0.182)	(0.139)	(0.109)	(0.262)	(0.152)	(0.127)
ln market potential		0.576***	0.395***	0.302**	−0.14	0.123	0.068	0.364**	−0.051
		(0.118)	(0.110)	(0.129)	(0.090)	(0.106)	(0.111)	(0.147)	(0.101)
ln distance			0.169	0.282**	0.276**	0.265	0.006	0.358**	0.352**
			(0.207)	(0.141)	(0.120)	(0.134)	(0.168)	(0.159)	(0.137)
Common language			0.949***	1.022***	1.022***	0.965***	0.854***	1.052***	1.053***
			(0.280)	(0.182)	(0.177)	(0.134)	(0.395)	(0.184)	(0.191)
Eastern Europe			−0.740**	−0.404*	−0.605**	0.047	−0.477	−0.397*	−0.636**
			(0.315)	(0.202)	(0.130)	(0.103)	(0.309)	(0.207)	(0.170)
ln unit costs				0.443***	0.592***	0.532***	0.595**	0.358**	0.519***
				(0.132)	(0.050)	(0.148)	(0.157)	(0.175)	(0.132)
ln corporate tax				−0.24	−0.401***	−1.222***	−1.090***	0.21	−0.065
				(0.346)	(0.127)	(0.172)	(0.236)	(0.408)	(0.202)
ln non-pharma investments					0.603***				0.579***
					(0.051)				(0.071)
ln RD expenditure						0.063			
						(0.042)			
ln # firms						0.552***			
						(0.082)			
Observations	14,229	13,650	13,650	11,130	11,130	10,739	2574	8556	8556
Log likelihood	−2160.83	−1560.549	−1525.519	−1350.462	−1309.037	−1759.336	−325.283	−1005.58	−977.351
Pseudo R^2	0.046	0.088	0.108	0.114	0.141	0.106	0.079	0.141	0.165

Standard errors in parentheses.
* Significant at 10%.
** Significant at 5%.
*** Significant at 1%.

Table 7
Comparing across types of investment.

	Dependent variable: location choice dummy							
	Estimation method: conditional logit							
	(1) Eastern Europe	(2) Western Europe	(3) Western Europe	(4) WE, manufacturing	(5) WE, R&D	(6) WE, other	(7) WE, other, excluding sales	(8)
Price regulation		−0.397***	−0.570***	0.051	−0.342	−0.645***	−0.386*	−0.486**
		(0.137)	(0.086)	(0.217)	(0.303)	(0.132)	(0.208)	(0.180)
Reference pricing	15.070***	−0.068	0.355***	0.028	−0.339	0.012	−0.306	0.018
	(0.843)	(0.225)	(0.104)	(0.380)	(0.242)	(0.205)	(0.275)	(0.177)
Therapeutic RP	−0.315	−0.159	−0.266	0.319	−0.217	−0.322	−0.541*	−0.565**
	(0.193)	(0.267)	(0.215)	(0.383)	(0.302)	(0.215)	(0.296)	(0.288)
ln market potential	1.505***	0.278**	−0.138	0.084	0.391**	0.272*	0.319	−0.038
	(0.250)	(0.124)	(0.085)	(0.126)	(0.202)	(0.150)	(0.163)	(0.129)
ln distance	−0.225	0.405***	0.446***	0.155	0.336	0.592***	0.557***	0.630***
	(0.579)	(0.126)	(0.093)	(0.181)	(0.221)	(0.180)	(0.153)	(0.165)
Common language		1.050***	1.051***	0.866*	1.112***	1.061***	0.838***	0.855***
		(0.182)	(0.174)	(0.460)	(0.142)	(0.233)	(0.277)	(0.276)
ln unit costs	0.742	0.415**	0.527***	0.681	1.326***	−0.042	0.454	0.447
		(0.069)	(0.068)	(0.438)	(0.507)	(0.207)	(0.286)	(0.449)
ln corporate tax	−0.776*	−0.160	−0.407***	−1.166***	−0.089	0.763*	0.993	0.639
	(0.485)	(0.323)	(0.129)	(0.294)	(0.398)	(0.415)	(0.668)	(0.430)
ln non-pharma investments			0.593***					0.493***
			(0.049)					(0.116)
Observations	414	6376	6376	1372	1635	3369	1039	1039
Log likelihood	−94.434	−1082.523	−1048.902	−234.162	−256.447	−565.743	−243.581	−239.117
Pseudo R^2	0.115	0.074	0.103	0.071	0.146	0.083	0.069	0.086

Standard errors in parentheses.
* Significant at 10%.
** Significant at 5%.
*** Significant at 1%.

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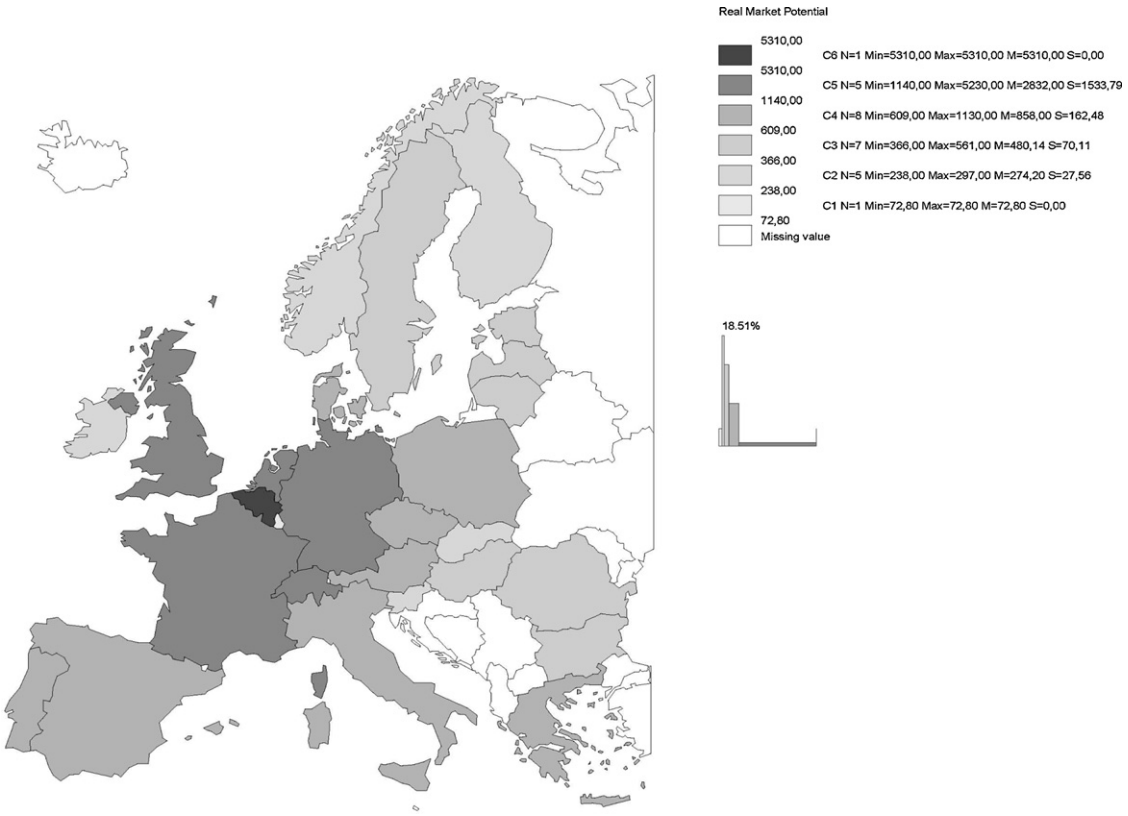

Fig. 3. Real market potential in Europe.

Table 8
Impacts of policy changes.

	Dependent variable: location choice dummy							
	Estimation method: conditional logit							
	Country fixed effects included							
	(1) Full sample	(2)	(3) Manufacturing	(4) R&D	(5) Non-manufacturing	(6) Non-MF/R&D excl. sales	(7) Benchmarking countries ≤7	(8) Benchmarking countries>7
Policy change	−0.910**	−0.892**	−1.005	−1.220*	−0.967***	−1.151**	−0.429	−1.229***
	(0.368)	(0.368)	(0.628)	(0.685)	(0.235)	(0.526)	(0.334)	(0.470)
Price freeze	−0.232**	−0.215**	−0.240	−0.419	−0.155	−0.694	−0.759	0.051
	(0.095)	(0.098)	(0.415)	(0.675)	(0.235)	(0.601)	(0.755)	(0.176)
ln market potential	−0.045	−0.081	−0.341	−0.201	0.399	0.296	0.261	0.218
	(0.350)	(0.359)	(0.834)	(0.678)	(0.378)	(1.516)	(0.629)	(0.457)
ln unit cost	0.286	0.286	0.920	0.445	−0.147	−0.042	0.817	0.206
	(0.807)	(0.761)	(1.530)	(8.487)	(1.251)	(2.496)	(1.885)	(0.834)
ln distance	0.210	0.211	0.023	0.189	0.363	0.346	−0.313	0.754
	(1.142)	(1.140)	(1.923)	(1.054)	(1.442)	(2.113)	(1.105)	(1.372)
Common language	0.969***	0.972***	0.763	0.918**	1.209**	1.360**	1.547**	0.908***
	(0.307)	(0.304)	(0.561)	(0.367)	(0.491)	(0.671)	(0.658)	(0.349)
ln corporate tax	−0.380	−0.207	0.361	0.221	−0.578	1.692	1.013	−0.559
	(1.622)	(1.511)	(2.666)	(7.910)	(3.192)	(5.011)	(1.896)	(1.520)
ln non-pharma investments		0.277*						
		(0.245)						
Observations	11,130	11,130	2574	2792	5764	1938	1585	3894
Log likelihood	−1290.141	−1288.592	−302.716	−274.618	−656.766	−206.757	−253.828	−741.935
Pseudo R^2	0.153	0.154	0.143	0.281	0.167	0.222	0.229	0.126

Standard errors in parentheses.
* Significant at 10%.
** Significant at 5%.
*** Significant at 1%.

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clearly difficult to estimate due to the small number of investments in these countries and little variation in the RP dummy, as evidenced by the very large coefficient on this variable.[20] In contrast to Eastern Europe, price controls are significantly associated with a 33% reduction in the odds of investment in Western European countries (column 2).[21] TRP regimes are not significantly associated with investment in the full Western European sample.

The distinction between Eastern and Western Europe may partly reflect the types of investment taking place in these locations. Indeed, we find that when restricting to Western European countries, price controls are not significantly related to investment for manufacturing or R&D announcements. For R&D investment (column 5), TRP is associated with a borderline (at the 5% level) statistically significant reduction of 44% in the probability of investment.[22] Price controls are, however, associated with a reduction in other types of investment statistically significant at the 1% level. The latter types of investment include headquarters, administrative offices, sales offices, logistical and distribution centers, and services to the firm.

Some of the latter investments may support the marketing of drugs to consumers. If countries with price controls are less profitable targets for marketing initiatives, we will expect to see less of this type of investment. In order to test the hypothesis that marketing efforts are driving the results, we drop from the analysis investments classified as follows: "Bureau commercial ou de liaison" (sales offices), "Commerce et services aux entreprises" (sales and services to firms), "Commerce et services aux particuliers" (sales and consumer services), "Point de vente" (sales location) and "Prestations de services" (provision of services). The results are presented in columns 7 and 8 of Table 7. We find that dropping these types of investments does indeed reduce the coefficient on price controls, and the standard error increases (note that omitting these observations results in the number of investments in this category falling from 258 to 85) so that the coefficient on price controls in column 7 is now significant only the 10% level. The effect of TRP regimes (calculated as the sum of the RP and the TRP coefficients) is −0.847, but is also only significant at the 10% level. However, after controlling for non-pharma investments in the destination country, the coefficient on price controls is more negative and is again significant at the 5% level, as is the coefficient on the TRP dummy. We will investigate this question further in the specification including policy changes and country fixed effects.

There are some additional interesting differences between the different types of investment. The corporate tax rate is strongly negatively associated with manufacturing investments but not the other types, while market potential is positively but insignificantly associated with manufacturing investment (evidence in favor of the "global market" hypothesis). Somewhat surprisingly due to our priors about the lack of importance of proximity to demand for R&D investments, market potential is positively associated with this type of investment. However, because market potential is so highly correlated with income and therefore education levels, it is possible that this positive coefficient reflects the attractiveness of destinations with many skilled workers. Note that when we control for non-pharma investments in the country, which captures the countries' general attractiveness for investment to other industries, the coefficient on market potential becomes insignificant and close to zero. Common language matters for R&D and other investments, reflecting the greater importance of communication barriers in these types of investment relative to manufacturing. The distance between the country of origin and potential destination countries is not significantly related to location choices for manufacturing and R&D investments, but it increases the likelihood of other investments (at the 10% level). The insignificance of distance for manufacturing again supports the view that proximity to demand matters little for this type of investment. The positive coefficient on distance for "other" investments may reflect incentives for the establishment of distribution centers and administrative offices associated with distant headquarters. Companies may be able to service neighboring countries from their base, but new facilities are required when expanding in more remote locations.

5.2. Results on price policy changes

The specifications presented in Tables 6 and 7 are informative about the general association between price regulation and FDI in European countries. In these specifications, we have controlled for many of the key drivers of location choice. However, it is possible that there are country-specific determinants of location choice that we have omitted and that are correlated with regulatory regimes. In order to guard against this possibility, country fixed effects should be included. However, given that the price control and reference pricing dummies are mostly constant throughout the sample period, it is difficult to measure their coefficients in a specification that includes country fixed effects. We thus exploit policy changes that took place during the sample period (listed in Table 2). Several countries made significant changes to their reference pricing regimes with the goal of reducing prices or froze or cut prices between 2002 and 2009. The results presented in Table 8 focus on these time-varying regulatory variables, and include country fixed effects. They resemble a "difference in differences" analysis, since we control for country-specific variation in the average level of investment through the country fixed effects, and identify the additional variation in investment that takes place in countries that change their policies relative to countries that do not change their policies.

We find that countries that reformed their pricing regimes during the period in question have a 59.7% lower probability of investment following the policy change than countries that did not change their policies (column 1 of Table 8). Price cuts or freezes are associated with a smaller, but still significant reduction in the probability of investment, on the order of a 21% decline in the probability of investment. When the data is broken down by type of investment, R&D investments see the largest percentage decline (column 4), but the coefficient is significant only at the 10% level. Most of the country characteristics are insignificant after controlling for country fixed effects, with the exception of the common language dummy, which varies by investor country and which has a strong positive association with the likelihood of investment. The results are robust to a control for the number of non-pharmaceutical investments, our proxy for the general level of attractiveness to foreign investment (see column 2). The results on non-manufacturing, non-R&D investments are also robust to dropping sales and marketing-related investments (column 6). This suggests that the decline in investment is not only related to lower incentives for marketing. However, if there are administrative activities related to marketing that are not classified as such in our data, the decline in investment could be explained by reduced marketing incentives.

In columns 7 and 8, we cut the data according to whether or not the set of destination countries is below the mean of the number of

[20] All of the 54 investments in Eastern Europe in this sample were made in countries and periods in which reference pricing was in force, and the latter observations constitute 92.5% of the Eastern European sample.

[21] Calculated as $\exp(\beta) - 1$.

[22] Note that since all countries with TRP also have RP regimes, the two coeffcients must be added together to interpret the effect of TRP. The variance of this sum as estimated in Column 5 is 0.083.

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Table 9
Results restricted to generics producers including all countries, types of investment, and investors.

	(1)	(2)	(3)	(4)	(5)	(6)
	No country F.E.s			Country F.E.s		
	Full sample	MF	Non-MF	Full sample	MF	Non-MF
Price controls	0.121	0.812	−0.299			
	(0.359)	(0.618)	(0.311)			
Reference pricing	0.469	1.100**	0.009			
	(0.603)	(0.546)	(0.658)			
Therapeutic RP	−0.438	−0.359*	−0.598			
	(0.300)	(0.214)	(0.620)			
Policy change				−0.598	−1.858	0.248
				(0.507)	(1.208)	(1.566)
Price freeze				0.498	1.486	0.344
				(0.644)	(2.035)	(2.282)
ln market potential	0.120	0.007	0.231	0.588	2.030	−0.166
	(0.214)	(0.301)	(0.216)	(1.328)	(4.503)	(2.681)
ln distance	−0.112	−0.384	0.269	−0.194	−0.670	0.301
	(0.163)	(0.176)	(0.294)	(0.355)	(0.450)	(0.532)
Common language	0.182	0.454	−0.383	0.232	1.068	−0.352
	(0.423)	(0.749)	(0.546)	(0.455)	(1.189)	(0.773)
Eastern Europe	−0.138	0.042	−1.605			
	(0.489)	(0.635)	(1.249)			
ln unit costs	−0.029	−0.157	0.372	−0.829	−0.815	−0.764
	(0.261)	(0.335)	(0.410)	(6.450)	(6.588)	(42.609)
ln corporate tax	0.842	0.294	1.120	1.643	3.404	−5.535
	(0.784)	(0.885)	(1.327)	(3.964)	(7.910)	(26.033)
Observations	2033	1060	973	2033	1060	973
Log likelihood	−343.489	−176.856	−150.559	−229.964	−107.954	−95.091
Pseudo R^2	0.023	0.039	0.102	0.141	0.229	0.255

Standard errors in parentheses.
* Significant at 10%.
** Significant at 5%. ***Significant at 1%.

other countries listing the country in their external price comparison groups (the mean and median are 7 countries). We find that the policy changes are only related to investment for the countries referenced by a number of countries at or above the average (the number of referencing countries is listed in Table 1). This finding supports our hypothesis that firms react most strongly to policy changes in high-profile countries, in other words, countries whose policies have the potential to affect prices in a larger number of other markets. It also suggests that increasing the stringency of the pricing regime will have no effect on investment in lower-profile countries (countries whose pricing decisions have little impact on prices across Europe).

Next, we consider the relationship between price regulation and investment by generics producers. Since these firms do not have incentives to attempt to influence policy by shifting investment away from countries with more stringent price controls, we do not anticipate that the negative relationship observed between regulatory stringency and investment by research-oriented firms will be repeated. If anything, generic producers may be more likely to locate in countries that tightly regulate prices of branded drugs because these countries have greater demand for generic drugs. In Table 9, we repeat our key regressions after restricting the dataset to generic firms. In the full sample (column 1 of the table), we find no significant relationship between regulatory policy and investment. However, when we restrict attention to investments in manufacturing facilities in column 2, we observe a positive relationship between price controls and investment (as predicted by the preceding argument about higher demand). Non-manufacturing investments are, as expected, insignificantly related to the policy regime. Columns 3–5 repeat the analysis of Table 8 including country fixed effects, and here we observe no significant relationship between policy changes and investment.

To summarize the results discussed above, we find that foreign investors are less likely to locate new investments in countries with explicit price controls than countries with reference pricing regimes or no price regulation. However, this finding is only observed in Western European countries and for non-manufacturing investments. The latter result may reflect stronger incentives for investments in marketing in countries in which prices are not directly controlled, rather than a strategic action by pharmaceutical firms seeking to send a message to countries with stringent regulatory regimes. When country fixed effects are included, so that we examine the change in investment patterns associated with changes in regulatory policy, we find that new investments significantly reduced in countries that imposed significant changes to reference pricing regimes after 2002, and that this finding appears to be driven by a reduction in non-manufacturing investments in countries whose prices have a broad impact on prices elsewhere.

The finding that non-manufacturing investments are particularly affected by regulatory regimes may at first seem surprising. One might ask why, if firms seek to influence government policy by re-directing investment to countries with more favorable regulatory regimes, they do not do so with manufacturing investments. Manufacturing facilities are less closely tied to the specific science or skill base of a location, and one would expect that firms would incur lower foregone profits in choosing a second-best location for manufacturing. However, if governments believe that new non-manufacturing facilities create more high-skilled jobs, contribute more to the tax base and generate greater spillovers for the region than do manufacturing facilities, they may be more sensitive to variations in the location of such investments. Thus the potential benefit in terms of political influence associated with the choice of non-manufacturing location may be greater, and this

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may partly explain why the effect is observed among these investments. However, when we distinguish between R&D facilities and non-manufacturing, non-R&D investments, we see similar effects for both types of investment. Many of the latter are likely to be related to marketing functions that become less important when prices are controlled more aggressively, so it is possible that part of the observed effect is due to reductions in sales staff or other marketing functions. If the results reflect reductions in marketing expenditures, then the normative conclusions to be drawn from this analysis are rather different. Less expenditure on marketing may actually be considered a benefit of price regulation rather than an unintended cost.

Is it possible that our results are explained by a geographically constrained link between demand and non-manufacturing investment? We do observe a positive correlation between market potential and R&D investment, which is consistent with the view that our results reflect a reduction in investment in countries that have become less profitable markets. However, if this is the story, we would expect the correlation between market potential in pharmaceuticals and investment to persist after controlling for the number of non-pharmaceutical investments in the country. The fact that market potential becomes insignificant when this control variable is added suggests that it is proxying for other factors attracting non-manufacturing investment such as the skill level of the workforce or public support for scientific research.

The reductions in investment we describe here are statistically as well as economically significant. Looking at the results reported in Table 8, for example in column 1, we see that countries that increased the stringency of their regulatory regimes during our sample period were approximately 59.7% less likely to receive an investment than countries that did not change their policies (holding constant time-invariant country characteristics).[23] On average, a given country receives 2.45 investments per year during our sample period, so a reduction of 60% would amount to approximately 1.47 fewer investments. The mean number of jobs reported to be created by an investment is 164.5 (although only approximately half of announcements report the number of jobs created). The effect of the policy change is comparable in magnitude to the effect of the origin and destination country sharing a common language, which increases the probability of investment by 54% (column 1 of Table 8).

It is difficult to obtain comprehensive evidence on the cost savings generated by the policy reforms that we analyze. German total expenditures on pharmaceuticals rose steadily from 26.4 billion euro in 1995 to 36.8 billion in 2003. After the inclusion of patented medicines in the reference pricing scheme, expenditures fell to 35.8 billion in 2004 (they rose again to 39.5 billion in 2005).[24] In Denmark, Kaiser et al. (2010) estimate a decline in patient and government expenditures on statins of 15 and 9%, respectively. At the time of the introduction of TRP in Hungary, the national health service anticipated savings of 4.30 billion forint (or $21.32 billion).[25]

Finally, we present some comments and results as additional robustness checks. First, because these announcements are voluntary public disclosures, there is a possibility that the dataset contains a disproportionate share of large, publicly traded firms. Since the R&D-performing pharmaceutical firms tend to be large and publicly traded, we are likely capturing a large majority of investments by these types of firms. However concerns about sample selection are likely to be more significant for smaller, privately traded biotech firms. It is important to keep in mind the sample composition when interpreting our results. If large, public firms are more likely to alter investment decisions in response to regulatory changes, our estimates will overstate the effect of regulation on investment by small, private firms.

Second, the data come from published sources in several languages. However, there is a possibility that because our data come from a French government agency, French-language publications may be over-represented in our database. We performed robustness checks on a dataset that excludes French-language publications, and obtained similar results. In response to a concern that investments in France or by French companies were over-represented in our data due to the origin of the dataset, we ran another set of regressions excluding investments made in France or by French companies, and again found similar results. These results are available upon request.

6. Conclusions

This paper examines the relationship between cross-country differences in drug price regulation and the location of biopharmaceutical FDI in Europe. We use data on 527 investments initiated in 27 European countries between 2002 and 2009 to estimate whether biopharmaceutical companies are influenced by the stringency of price regulations in choosing the countries in which to locate new investments. We find that countries with price controls receive fewer new non-manufacturing investments, after controlling for other determinants of investment. Countries that increased the stringency of price regulation during the sample period were relatively less likely to receive an investment after the policy went into effect. However, these effects vary across type of investment, with the most robust negative effect observed for administrative investments, only weakly significant effects for R&D, and no effect for manufacturing investments.

Appendix A. Drug price regulation data

Information on regulatory policies by country come from a variety of sources. The starting point was Table 2 of Kyle (2007a). This was supplemented with information on a larger set of European countries and a later time period using the following sources. Of particular value are the country profiles made available by the Pharmaceutical Pricing and Reimbursement Information (PPRI) Program, at http://ppri.oebig.at/index.aspx.

Information on policies across countries was also obtained from:

Vogler, S., Espin, J., Habl, C., 2009, Pharmaceutical pricing and reimbursement information (PPRI) – New PPRI analysis including Spain. Pharmaceuticals Policy and Law 11, 213–234.

Additional information on countries' policies came from:

Adamski, J., Klim, A., Splawinski, J., 2008. Cost containment in the pharmaceutical sector: Innovative approaches to contracting while ensuring fair access to drugs. Presented at Peer Review Meeting, European Commission DG Employment, Social Affairs and Equal Opportunities, June 30 to July 1, 2008.

Danzon, P., Ketcham, J., 2003. Reference pricing of pharmaceuticals for medicare: evidence from Germany, The Netherlands and New Zealand. National Bureau of Economic Research, Working Paper 10007.

Ferragut Ensenyat, G., 2007. Update on pharmaceutical policy in Spain. Health Policy Monitor (10).

[23] This is the result of the comparison of the ratio of the probability firm i invests in reforming country r (P') to non-reforming countries (P): P'/P. Since these two estimated probabilities differ only by $\exp(\beta)$ where β is the coefficient on the "policy change" dummy, and the latter coefficient is −0.91, we estimate that the probability of investment in reforming countries is approximately 40.3% of that in non-reforming countries.

[24] PPRI Country Profile – Germany (2008), p. 27.

[25] *The Pharma Letter*, July 4, 2005.

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