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The National Regulation of Pharmaceutical Markets

and the Timing of New Drug Launches in Europe

by

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Abstract

We analyze the impact of national pharmaceutical regulation on the launch delay of new chemical entities approved by the EMEA's centralized procedure. We find that direct price control regimes have a significantly negative impact on the launch timing. These results cannot be found when investigating the impact of indirect price controls. Our results show that Germany (65%) has the highest probability of experiencing an early launch, while it is the lowest in southern European countries (18% for Portugal and 19% for Greece). This difference accrues from both price regulation and market attractiveness, since southern European countries generally have lower prices. Due to the possibilities for parallel trade within the EU, pharmaceutical companies, by acting strategically, may further increase launch delays.

Keywords: pharmaceuticals, regulation, new chemical entity, parallel trade
JEL classification: I11, I18, L51

1 Introduction

The current regulatory situation in the pharmaceutical market of the European Union (EU) is very diverse. The construction of a single pharmaceutical market has been partially achieved. Market authorization has been harmonized, resulting in the introduction of the centralized procedure and the mutual recognition procedure that provide pharmaceutical firms with access to the large EU market. Nevertheless, control over pharmaceutical prices still remains with national authorities and partly contributes to the large price differences between the Member States. This complex regulatory situation leads to substantial disruptions throughout the EU: It creates the opportunity for parallel trade and influences the launch timing of new drugs. This can have negative welfare implications.[1]

With the introduction of the European Medicines Evaluation Agency (EMEA) in 1995, the EU Member States wanted to harmonize access to the pharmaceutical market. A common European market in pharmaceuticals benefits both patients and companies: Patients have better access to all drugs available within the EU and companies benefit from a larger market after authorization.

With the EMEA, market authorization for the entire EU market can be achieved via the centralized procedure (CP).[2] The European Commission approves market authorization, following the recommendations of the EMEA. Thus, a centrally authorized drug can be marketed in all Member States. The CP is required for biotechnology products as well as for orphan drugs and optional for other pharmaceuticals.[3]

Compared to the preceding regulatory framework, with the need for approval in every single country, the new procedure facilitates EU-wide market authorization, thereby leading to a decrease in overall launch delays.[4].

However, market authorization is not the only factor explaining launch delays: After it is granted, firms still have to submit the price or reimbursement approval. Danzon et al. (2005) suggest that the launch delay of new drugs is primarily due to price regulation, rather than market authorization. They analyze drug launches of 85 NCEs

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[1]Lichtenberg (2005), analyzing the impact of new drug launches on longevity, finds that the average annual increase in life expectancy is 0.56 years, or 29.3 weeks.

[2]Market authorization can also be achieved via the mutual recognition procedure where firms demand authorization in one Member State and file for mutual recognition in other countries. However, our analysis only focusses on the centralized procedure.

[3]Orphan drugs treat rare diseases.

[4]CMR International (2001) analyzes different regulatory authorities in the major markets and finds that the CP has led to a reduction in market approval times (to around 15 months)

launched in 25 major markets between 1994 and 1998. Their results indicate that countries with lower expected prices or a smaller market size have fewer launches and also longer launch delays.[5] Nevertheless, their study does not explicitly test for the impact of different regulatory regimes on the launch delay. This is the center of our analysis.

We focus on NCEs approved by the EMEA's centralized procedure between 1995 and 2004. All drugs that were approved by this procedure have achieved market authorization for the entire EU market. This implies that the varying launch delays did not come from the authorization procedure, but must have been due to different national price or reimbursement regulations. Thus, the approach allows us to clearly separate the impact of the different national price regulations from the impact of the market authorization regulation. We test how different systems of price and reimbursement regulation affect the probability of an early launch of new drugs. Even if European market authorization is granted, firms may not want to launch their products in all Member States' markets immediately. The rationale behind choosing this strategy and forgoing sales, even though the patent continues to run, can be direct and indirect price controls as well as the potential for parallel trade.

We find that the use of international price comparisons has a significantly negative impact on the timing of new drug launches. Indirect price controls do not seem to contribute to the varying launch delays, at least for on-patent drugs. Southern European countries generally experience longer launch delays. These countries are not only less attractive markets due to lower GDP (per capita), but also the markets are more regulated.

This paper is organized as follows: Section 2 analyzes the regulatory framework and the firms' strategic behavior. Section 3 and 4 cover the data and the econometric model. Section 5 presents the results. Section 6 concludes.

2   Regulatory framework

The pharmaceutical market is characterized by various market imperfections. The development of a pharmaceutical product involves large expenses for R&D. These costs are fixed and independent of the number of people or countries that will use the drug in the future. Patent protection grants to a firm temporary monopoly power to cover

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[5]Within the EU, the six countries with the largest delays (Portugal, Italy, France, Belgium, Spain and Greece) are those with strict price control.

the expenses of R&D. On-patent drugs are not exposed to competition from generically equivalent products until the patent expires. On the other hand, patients having extensive insurance coverage become price indifferent. The existence of insurance provides incentives for higher consumption of drugs and facilitates the application of higher prices (moral hazard).

To contain the costs of the national health insurance system, countries employ direct and indirect price controls. While direct price controls target the price of a pharmaceutical, indirect price controls are generally used to regulate its reimbursement level. If regulatory regimes have a negative impact on the expected value of the profits, products may either not be launched at all or launched with delay. This can have adverse consequences for the health and the welfare of the population (Lichtenberg, 2005).

In the following two sections we discuss the impact of direct and indirect price controls on the pharmaceutical firms' launch decisions.

2.1 Direct price control

Direct price controls are used by every EU country, except Germany and the UK. They consist of setting or negotiating a maximum price, a so-called price cap, for which a certain drug can be sold in one country. The price cap is set before a product is launched in the market. Prices may not exceed this level. However, pharmaceutical firms are allowed to undercut the set prices. In some cases they might even be forced to charge a price below the price cap to avoid losing market shares. If a drug with similar therapeutic properties enters the market or the patent of the drug expires, generic substitutes will begin to compete with the originator's product (Brekke, Königbauer and Straume, 2006).

To determine the maximum price, international price comparisons are frequently used. International price comparison implies that, while setting the price for a drug, national authorities take into account the price of the same drug in foreign countries. Some countries set prices following a well-defined rule, based on an index of foreign prices. In other countries, foreign prices are only taken into account as a basis for their decision making criteria.[6]

Furthermore, the choice of referred countries differs. In many cases there is mutual or even circular referencing. Table 1 gives examples of international price comparisons

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[6]Countries using an index include Austria, Greece, Ireland, Italy, Luxembourg, the Netherlands and Portugal. Countries using foreign prices as a basis inlcude Belgium, Finland, France, Sweden (until 2002), Denmark and Spain (Stargardt and Schreyögg, 2006; Rovira and Darba, 2001).

within the EU.

Table 1: International price comparisons in selected EU countries

Country	Method
Belgium	Ex-manufacturer's price in France, Germany, Luxembourg and the Netherlands
Denmark	Average European ex-manufacturer's price excl. Greece, Portugal, Spain and Luxembourg, but incl. Liechtenstein
Finland	Average EU wholesale price
Greece	Lowest price in Europe
Ireland	Average wholesale price of Denmark, France, Germany, the Netherlands and the UK
Italy	Weighted average ex-manufacturer's prices in EU (excl. Luxembourg and Denmark)
Netherlands	Average ex-manufacturer's price of Belgium, France, Germany and the UK
Portugal	Minimum ex-manufacturer's price of identical products in France, Italy and Spain
Spain	Country of origin; lowest price in the EU

Source: Mrazek and Mossialos, 2004; Kucher, 2000

Possible adverse effects and welfare losses arise from the combination of international price comparisons and the profit maximizing behavior of multinational pharmaceutical firms. Countries import prices from those countries that they use as reference countries. This interdependence leads to the possibility of exporting low prices to countries with generally high prices.[7] Domestic prices in high-price countries are undermined, which lowers the overall profits of the firms. Since firms want to maximize the expected net revenue across all potential markets, there is a trade-off between not launching a drug in a country with low prices and forgoing turnover in this country, and being able to charge a higher price in another country (Danzon and Towse, 2003). Consequently, if a country with low drug prices is used by another, high-price country as a reference country, then the low-price country will experience longer launch delays. This effect should be more pronounced, the higher the expected sales volume in the country with the higher prices.

Apart from international price comparisons, other means are used to negotiate prices. These include taking into account the therapeutic value of the drug, the cost of comparable treatments or the pharmaceutical's contribution to the economy as well as cost-effectiveness pricing. The therapeutic value of the drug is taken into account by Belgium, Finland, France, Spain and Sweden. These countries also look at the costs of comparable treatments. Recently, some countries require cost-effectiveness studies in their New Drug Application (Jacobzone, 2000). Sweden changed its regulatory

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[7]Higher prices stem from greater willingness or ability to pay. Jacobzone (2000) identifies Germany, the US and Switzerland to have relatively high prices, whereas Italy, Spain, Portugal and Greece have rather low prices. The UK, the Netherlands and recently France are considered to have intermediate prices.

scheme in 2002, abandoning the use of international price comparisons. Since then, cost-effectiveness is one important principle in the Swedish regulation system. By calculating the cost-effectiveness of a new drug, Sweden first looks at all costs associated with using the drug (costs of the drug, doctoral visits, further healthcare measures, costs of side-effects). These costs then are balanced to the benefits of using the drug, which come in two forms: effects on health and cost savings. The beneficial effects on health show up either as a longer life expectancy or as a higher health-related quality of life. From the societal perspective, it also has to be taken into account if the use of the new drug means that the patient will be able to work and support herself in the future instead of being sick-listed and perhaps forced into early retirement. With this type of analysis, the regulator is able to justify whether or not the use of the new drug costs the citizens more than the patient gains (Tauberman, 2005). The contribution of the pharmaceutical to the economy, e.g. the number of employees involved in the production or distribution of the drug, is taken into account by Belgium and Spain. Regarding the analysis of the timing of new drug launches, we would expect highly regulated markets to have a lower probability of an early launch.

2.2   Indirect price control

There are two main types of indirect price controls: profit control and reference pricing (RP). Profit control constrains the profit margin at which the companies may operate. They are allowed to set their own prices but cannot exceed a certain profit ceiling which is negotiatied between industry and government representatives. In our sample, the United Kingdom is the only country using profit control.[8]

Reference pricing has gained popularity as a price control mechanism during the last 20 years. In Europe, it was first introduced by Germany in 1989 and later applied in the Netherlands (1991), Sweden and Denmark (1993), Italy (1996), Spain (2000) and Belgium (2001). While Portugal (2003) and France (2004) also introduced reference pricing, Sweden abandoned it in October 2002.[9]

The purpose of reference pricing is to limit the rise in pharmaceutical expenditure by setting the reimbursement level. On the demand side, reference pricing creates an incentive for patients to be more price sensitive and therefore decreases the demand for

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[8]The rate of return on capital for a pharmaceutical company is targeted at around 17 - 21% with a 25% margin of tolerance (Jacobzone, 2000).

[9]Outside Europe, reference pricing has been adopted in Australia, British Columbia (Canada) and New Zealand.

high-priced products.[10] On the supply side, reference pricing stimulates price compe-
tition between pharmaceutical firms that, facing the threat of losing market shares,
react by cutting prices.

National authorities fix reimbursement levels for products grouped in one cluster. The
construction of the clusters may influence the launch decision. We can define three
different types of clusters: the first type includes products with the same active in-
gredient, the second type includes products with chemically related active ingredients
that are pharmacologically equivalent, while the third type includes products that may
be neither chemically identical nor pharmacologically equivalent but have comparable
therapeutic effects.[11] The first type includes only off-patent brand name drugs and
their generic substitutes. The second and the third type may include on-patent drugs.
Following Brekke, Königbauer and Straume (2006) we refer to the first type as generic
reference pricing (GRP) and to the second and third type as therapeutic reference
pricing (TRP).

GRP and TRP differ in their outcomes. Several studies show that TRP reduces patent
rents, making global innovation and market entry less likely (Danzon, 2001; Brekke,
Grasdal and Holmås, 2006; López-Casasnovas and Puig-Junoy, 2000). The impact of
GRP on the timing of new drug launches is ambiguous. Danzon (2001) argues that it
creates price competition only between off-patent drugs, thus having a minimal adverse
effect on incentives for innovation. On-patent drugs are not exposed to competition
from generically equivalent products until the patent expires, so that a substantial
part of the R&D expenses is covered. Brekke, Grasdal and Holmås (2006), studying
the impact of the introduction of reference pricing on the launch of therapeutic sub-
stitutes in Norway, find that the price competition induced by GRP may negatively
affect a patent-holding firm, even though its on-patent drug is excluded from the RP
system. Faced with competition from therapeutically equivalent off-patent drugs, the
patent-holding firm may be forced to lower the drug price in order to avoid a loss of
market shares. Nevertheless, this cross-price effect seems to be weak since the drugs
have different chemical substances and are only imperfect substitutes. Furthermore,
Lichtenberg and Philipson (2002) find that between-patent competition (therapeutic
competition through the introduction of a new product under a new patent) costs the
innovator at least as much as within-patent competition (generic competition), which
cannot occur until a drug is off-patent. This is due to the fact that a patent only hin-

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[10]Demand becomes price elastic only above the reimbursement level.

[11]Pharmacologically equivalent means that they have similar interactions with the human body.

ders others to produce the same product but not to produce a better product within the same disease or drug class. Thus, even if a negative cross-price effect from GRP exists, therapeutic competition seems to be more harmful than generic competition.

All countries but the Netherlands, which uses both types, only use generic reference pricing, such that on-patent drugs are not subject to a reference pricing system. If a negative cross-price effect of GRP on on-patent drugs exists, we would expect a longer launch delay in countries using a system of reference pricing.

To summarize the direct and indirect price controls, Table 2 gives an overview of the regulatory systems used in the analyzed countries.

Table 2: National pharmaceutical regulation in EU15 countries

Country	Direct control				Indirect control	
	Free pricing	International comparison	Therapeutic value/ Cost-effectiveness	Pharmaceutical contribution	Profit control	Reference Pricing
Austria		since 2004	✓			
Belgium		✓	✓	✓		since 2001
Denmark	until 2003	since 2003				✓
Finland		✓	✓			
France		✓	✓			since 2004
Germany	✓					✓
Greece		✓	✓			
Ireland		✓	✓			
Italy		✓	since 1997			since 1996
Luxembourg		✓	✓			
Netherlands	until 1996	since 1996	since 1996			✓
Portugal		✓	✓			since 2003
Spain		✓	✓	✓		since 2000
Sweden		until 2002	✓			until 2002
UK	✓				✓	

Source: Jacobzone, 2000; Mrazek and Mossialos, 2004; Kucher, 2000

2.3   Parallel trade

As we have argued above, drug prices differ across countries due to different regulation schemes. This means that the same, centrally approved, drug is sold in different countries at different prices. Together with the principle of the free flow of goods in the EU, this gives rise to arbitrage and parallel trade can occur: Wholesalers have incentives to buy a drug in a low-price country and resell it in a high-price market. The European Court of Justice confirmed in several cases that the free flow of goods overrides the principle of national exhaustion of patents. Thus, it is legal to import an on-patent drug and resell it without having permission from the patent-holder. The volume of

parallel trade is estimated to amount to EUR 4.2 billion in 2004 whereas the share of parallel imports in pharmaceutical market sales ranges from 2% (Finland) to 17% (UK) (EFPIA, 2006).

In general, one would expect that consumers or the national health insurance system benefit from parallel trade due to lower drug prices. However, Costa-i-Font et al. (2004) analyze six European countries and find that the savings from parallel trade are modest and only the traders gain.[12] Nevertheless, a similar study from the University of York finds total savings of EUR 631 million for five European countries (Mahon and West, 2003).[13] Comparing these two studies, Enemark et al. (2006) conclude that the methodology applied by the University of York is more appropriate. Using a similar approach, they find total savings in four European countries to amount to EUR 441.5 million in 2004.[14] Thus, these studies indicate that either the national health insurance system or the traders benefit from parallel import. On the other hand, the drug producer always suffers a loss if parallel trade occurs.

The introduction of the EMEA's centralized procedure for market authorization has further facilitated parallel trade. Package or labeling differences previously hindered parallel trade by increasing a trader's costs of repackaging and labeling. In the centralized procedure, standardized drug dosages are approved in all Member States. This reduces a trader's costs and facilitates the occurence of parallel trade.

Ganslandt and Maskus (2004) identify southern European countries such as Greece, Italy and Spain as major parallel exporters. As a result, pharmaceutical firms may delay launch in these countries to avoid losses due to parallel trade.

3   Data

Our data are taken from the IMS Drug Launches database, known as the IMS New Product Focus. It reports new drug launches in 60 major markets of the world, with data on their NCE status, trade name, active ingredients, marketing company, anatomical therapeutic chemical code (ATC), launch date etc. We are interested in the launch experience of NCEs within the (former) EU15. We focus on launches in the outpatient (retail) sector because this accounts for roughly 80% of the total drug sales in most countries. Furthermore, national price regulation aims at prices for the outpatient sec-

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[12]The analyzed countries are Denmark, Germany, the Netherlands, Norway, Sweden and the UK for the year 2002.

[13]Denmark, Germany, the Netherlands, Sweden and the UK for the year 2002.

[14]Denmark, Germany, Sweden and the UK.

tor and prices for the hospital sector are negotiated differently.

Using the IMS database we identified a total of 132 NCE launches in the EU15 countries between January 1995 and December 2005. Of these, only 43 were approved through the EMEA's centralized procedure. We excluded five NCEs because they were not launched in the outpatient sector. To allow for a minimum observation period of 12 months for the launch delay, one additional NCE was excluded because it was only approved after December 2004. Furthermore we excluded Bondronat from the sample of NCEs. The EMEA reports its date of approval for 1996 whereas the marketing company announces approval only in 2001. In some countries it was launched shortly after the approval in 1996, while in other countries exceptionally high launch delays occured. We also excluded Insuman since it was only launched in Germany. Thus, our final sample consists of 35 NCEs approved by the EMEA's centralized procedure between January 1995 and December 2004. This results in 35 times 15 potential launches within the EU15.

We exclude Luxembourg since its country profile presents an extreme outlier among our sample. It has the highest GDP per capita and the smallest population size. Furthermore, there is no independent pharmaceutical regulation. Luxembourg imports all of its pharmaceuticals, thereby only adopting the prices of Belgium, France or Germany.[15]

Table 3 shows summary statistics for the drug launches in the analyzed countries.

From the potentially 490 launches only 332 occured. Germany (33), the UK (31) and Denmark (29) experienced the most launches, while the fewest launches occured in Portugal (13). The average launch delay in each country ranges from 3.5 months in Germany to 18.9 months in Belgium, with an overall average delay of 10.3 months. The maximum delay goes up to 50 months in several countries (Portugal, Italy, Greece, France, Belgium) with the highest observed delay occuring in Sweden (88 months). The table also shows the number of launches that occured within 8 (10, 12) months after the first launch in a country was observed. For example, in France 22 NCEs were launched, but only 7 within the first 8 months after the approval date. The column for first launch indicates in how many cases the country was the first market for the new drug to be launched. It shows that Germany, with a relatively unregulated market, was chosen 20 times as the first market to launch a new product.

Pharmaceutical companies may have incentives to launch earlier in their country of

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[15]The existing direct price control only examines if the price of the drug in these countries is reasonable.

Table 3: Summary Statistics

Country	N	Launch delay in months				Drugs launched within			1st launch
		Mean	SD	Min	Max	8 months	10 months	12 months	
Austria	23	6.4	6.6	0	26	17	18	21	1
Belgium	23	18.9	13.1	1	49	5	5	7	0
Denmark	29	8.7	10.4	0	47	18	19	22	3
Finland	26	7.7	8.0	0	35	16	19	21	1
France	22	15.2	12.5	0	50	7	7	9	2
Germany	33	3.5	5.2	0	20	29	30	30	20
Greece	19	13.4	13.1	3	54	8	12	12	0
Ireland	25	9.8	11.7	0	40	16	17	18	1
Italy	25	17.5	13.3	2	50	8	9	12	2
Netherlands	18	4.9	4.8	0	19	15	17	17	5
Portugal	13	14.2	13.8	0	53	4	7	8	0
Spain	25	13.5	10.5	1	41	12	13	16	0
Sweden	20	7.9	19.4	0	88	15	16	18	3
UK	31	8	9.9	0	38	19	20	25	10
TOTAL	332	10.3	11.9	0	88	189	209	236	

origin compared to a foreign country. They might have more or better information about the regulatory procedure. Furthermore, they may be treated differently during the negotiation process. To analyze whether there is home bias in launching new products, we compare the average launch delays for NCEs launched by domestic companies and foreign companies. From the 35 NCEs, 19 were launched by a company originating from Switzerland or the USA. Seven launches occured by French companies, whereas six launches occured by German companies. Only one NCE was originating from the Netherlands, Denmark and Finland, respectively, and they are therefore not analyzed. Switzerland and the USA are not part of our sample, so we cannot analyze a potential home bias in these markets. By comparing German and French NCEs, we try to find evidence for home bias in these markets: The average delay for French companies launching in the French market is 14 months, while it is 15.6 months for companies from outside France. In Germany, the average launch delay for German companies is 2.2 months, while it is 3.8 for foreign companies. Thus, in both markets, the average delay is lower for domestic companies. Since the differences are very small, we assume that home bias is not present.

4   Econometric model

In order to estimate impacts on the launch delay of NCEs, we apply a binary response model with an underlying standard normal distribution, i.e. a probit model. The descriptive statistics presented in the previous section show that 189 out of 332 NCE launches already took place within eight months of the approval date. As a reference, we therefore take a period of eight months after approval. Our binary endogenous variable is defined as

$$Y = \begin{cases} 1 & \text{if the drug was launched within 8 months,} \\ 0 & \text{otherwise.} \end{cases} \tag{1}$$

For our estimation we use a simple probit model of the form

$$P(Y = 1|\mathbf{x}) = \Phi(\mathbf{x}'\boldsymbol{\beta}) \tag{2}$$

where Φ is the cumulative distribution function of the standard normal distribution. This model allows us to explore how each explanatory variable affects the probability of the drug being launched within our reference period.

In the first model we test for general country characteristics such as GDP per capita, drug expenditure, population size and structure as well as health indicators. Since country characteristics vary over time we assigned the respective characteristics at the date of launch for drugs launched within eight months. If a drug was not launched within the reference period or not launched at all, we assigned the country characteristics at the point of reference, i.e. eight months after approval. We do so to account for the conditions that were relevant for the company's decision at the time of launch. The problem of potential heteroscedasticity is solved by grouping the observations into 14 country clusters.

In addition to the country characteristics variables, our second model also includes variables explaining the regulatory framework. From Table 2, which describes different pharmaceutical regulations, we derived three dummy variables. The first variable controls for the use of international price comparisons. The second variable (Other DPC) indicates the use of other direct price controls, such as therapeutic value of the drug, cost-effectiveness or pharmaceutical contribution to the economy. The third variable controls for the application of reference pricing. We cannot explicitly test for the impact of profit control since it is only used in the UK, yielding a problem with the clustering of observations into countries. We also do not include free pricing as a variable because it is implicitly given by the other variables.[16] For the varying regulatory

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[16]A country only using indirect price controls automatically applies free pricing.

framework, we apply the same assignation rule as in the country profile model.

In a third model, we further differentiate the use of international price comparison. We build two variables of international price comparison, one indicating the rule-based use of an index of foreign prices (Index), whereas the other variable includes countries using foreign prices only as a basis for their decision making criteria (Basis).

5 Results

Table 4: Probit model results

Variable	Country model	General regul. model	Detailed regul. model
ln(GDP/cap)	0.643*	0.222	0.128
Population	0.022***	0.009	0.008
Int. Comparison		-0.463*	
Other DPC		-0.304	-0.293
Reference pricing		0.136	0.173
Int. Comp. Index			-0.584***
Int. Comp. Basis			-0.442*
Const.	-13.760	-8.989	-7.424
N	490	490	490
Chi^2	44.995	88.398	80.065
AIC	624.911	621.870	623.133
Pseudo R^2	0.065	0.079	0.080

$^*p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$

Country model Table 4 presents the results of our estimations.[17] In the country model we analyzed the impact of different country characteristics such as GDP, population and health indicators. Most of the coefficients had the expected sign. However, only GDP per capita and the size of the population were statistically significant. Both a higher GDP per capita and a larger population indicate a big potential market and therefore have a positive impact on the probability of an eary launch. Life expectancy, drug expenditure, percentage of the population above 65 as well as the death rate were not significant and are therefore not reported in the table.

General regulation model In order to separate the effects of particular regulation schemes we estimate a second model including variables for the regulatory scheme. The

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[17]To check for robustness, we also estimated the model for a period of 10 months delay. The signs of the coefficients did not change. The reported values only differed marginally.

coefficients for GDP per capita and population now become insignificant.

Countries using international comparison to determine their prices experience a significantly lower probability of launch within the first eight months than countries that do not use it. However, we are not able to model the effect of being a reference country. It depends on the price level in the reference country compared to the referring country. For example, Germany is almost always included in the international comparison scheme. Being a high price market, this should further shorten launch delays in Germany. If low-price countries like Greece and Spain are taken as a reference country, they should experience longer launch delays.

The coefficient for other direct price controls has the expected sign but is statistically insignificant. Reference pricing has a positive effect, but is also not significant, indicating that the cross price effect seems to play no role in determining the probability of experiencing a launch delay.

Given the estimated coefficients, we calculated the probability of success for an early launch under different regulatory schemes, shown in Table 5.

Table 5: Probability of success

	Int. Comp.		Basis		Index	
x	**1**	**0**	**1**	**0**	**1**	**0**
P(Y = 1|x)	33.0%	50.9%	27.5%	43.8%	24.7%	46.0%

Using international price comparisons yields a 33.0% chance of launch within eight months. All else equal, if a country abolished the use of international comparisons to determine prices, the chance of success would rise to 50.9%.

Detailed regulation model   In our last estimation we consider that also the design of the international price comparison may matter and include different variables according to the regulatory scheme. Both international comparison based on an index of foreign prices and using international prices as a basis for the decision have a negative impact, with the first being insignificantly stronger.[18]

The calculated probabilities of success for the two new variables are also given in Table 5. A country using a rule for international price comparison has a 24.7% chance of experiencing an early launch. If it were not using this type of regulation, this chance would ceteris paribus rise to 46.0%. The effect of using international prices as a basis

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[18]We cannot reject the Null-Hypothesis of equality of the coefficients in a Wald-Test at the 1% level.

for the price cap lowers the probability of an early launch from 43.8% (not using international prices as a basis) to 27.5% (using international prices as a basis).

This difference may stem from the fact that, if a strict rule is applied, there is less room to negotiate higher prices and companies therefore rather delay the launch of new products.

Summary We calculated the average predicted probability of experiencing an early launch in every country, using the results from the general regulation model.[19] The results are presented in Table 6.

Table 6: Country probability of success

Country	Probability	Rank	Country	Probability	Rank
Austria	43.2%	6	**Ireland**	45.2%	4
Belgium	24.1%	12	**Italy**	28.4%	11
Denmark	59.4%	3	**Netherlands**	45.0%	5
Finland	29.3%	10	**Portugal**	17.8%	14
France	29.8%	9	**Spain**	32.9%	8
Germany	65.4%	1	**Sweden**	36.0%	7
Greece	19.3%	13	**UK**	63.8%	2

As expected, Germany has the highest probability with 65.4%. It is followed by the UK (63.8%) and Denmark (59.4%). We find the lowest probabilities for Portugal (17.8%), Greece (19.3%) and Belgium (24.1%). Inbetween, there is not much variation with probabilities in the 30%-range for the other countries. It is striking that the countries with the highest probability of launch are also the countries that impose the lowest regulation on pharmaceutical prices. Germany and the UK are the least regulated markets, both using only indirect price controls (reference pricing in Germany, profit control in the UK). Denmark used free pricing in combination with reference pricing until 2003, when this regulation was substituted by the use of international price comparisons. Table 1 shows that Denmark is the only country that excludes the relatively low-price countries from its international comparison scheme. Thus, even though it abolished free pricing in 2003, the new regulation does not seem to induce low prices, giving companies incentives to launch early.

France and Italy have a significantly lower probability of an early launch than Germany. Since they are comparable markets in terms of GDP (per capita), the difference should come from the higher level of regulation.

The low probability for Belgium may stem from the fact that Belgium, together with

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[19]Using the detailed regulation model yields similar probabilities.

Spain, is using the most available instruments for regulation (Table 2).

The expected delays in Portugal and Greece could be due to the strict regulation of prices. Table 1 shows that these countries rather use low price countries for their international comparisons which intensifies the downward pressure on prices (in addition to country characteristics, such as GDP per capita and others). Mutual referencing between these countries and the proliferation of low prices it causes, further deters firms from an early launch. The resulting low expected prices make these countries potential parallel exporters, as identified by Ganslandt and Maskus (2004). Thus, by avoiding early launches in these countries, companies are able to charge higher prices in other countries, without having to compete with parallel imported drugs.

6   Conclusion

This paper analyzed the effects of different national regulatory regimes on the timing of new drug launches in Europe. We focused on NCEs approved by the EMEA's centralized procedure between 1995 and 2004. This approach allowed us to separate the effects of national regulations from the impact of the market authorization procedure. Apart from country characteristics such as GDP (per capita), the inconsistency in the price regulatory schemes plays an important role in determining the launch timing.

Estimating three probit models, we found that among the direct price controls, only international price comparisons have a significantly negative impact on the launch timing. Other direct price control mechanisms, such as therapeutic value of the drug or the cost of comparable treatments as well as cost-effectiveness pricing, do not seem to play an important role.

Regarding indirect price controls, we did not find evidence for a negative cross-price effect stemming from generic reference pricing. However, since we only analyzed on-patent NCEs, we cannot derive any conclusions regarding its impact on generic products.

One limitation of this study comes from the lack of information on the regulatory framework which had to be collected from multiple sources. Within the Pharmaceutical Pricing and Reimbursement Information (PPRI) project of the European Commission and the WHO, detailed information on national regulatory systems are currently collected. This single-sourced information can be used for a more detailed analysis in the future.

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