Explaining Early Adoption on New Medicines: Regulation, Innovation and Scale

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Abstract

Understanding how price regulations affect the adoption of new patent-protected pharmaceutical technologies is a crucial question in designing health systems. This paper addresses this question by examining how price expectations shape the probability of launch, controlling for competition, market size expectations, firm and molecule heterogeneity across the major OECD markets during 1999-2008. Due to the censoring of launch data we use discrete time duration modelling with parametric and semi-parametric duration dependence specification. A sub-sample analysis including only EU countries also investigates the impact of price interdependencies and potential firm strategies in launch and pricing decisions. The empirical analysis of the global set of molecules which have diffused across more than 10 markets in the OECD, suggests there is a statistically significant and robust price effect in the adoption of new pharmaceutical technologies; low-prices result in reduced and slower adoption. Concentrated therapeutic subgroups, reflecting market crowding constitutes a significant barrier to entry. Sub-sample findings from the EU market suggest strategic firm behaviour with firms delaying launch in low-priced markets and attempts to maintain price differentials across interdependent markets to a minimum due to price complementarities. Firm economies of scale and the therapeutic importance of innovations are other important drivers of adoption speed.

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1 INTRODUCTION

 International launch strategy of new pharmaceuticals, i.e. timing and order of market entry, is compounded with difficulties due to the unique and often country-specific regulatory nature of the pharmaceutical industry. The majority of the countries in the OECD employ pricing and reimbursement (P&R) controls to contain costs, promote rational drug use and less frequently to protect the local industry against international competition. The recent financial crisis and fiscal austerity measures to tackle budget deficits are driving the need for even more stringent price controls. While there is a small literature on the effect of regulation on drug prices and competition, the evidence regarding the impact of regulation on the launch timing of pharmaceutical innovation is scanty.

The aim of this paper is to improve our understanding of the effects of regulation on the speed of adoption of new pharmaceutical products (adoption in this paper is specified by the first launch date of a given molecule). The impact of regulation on entry and social efficiency has been highlighted by various economists (Djankov et al., 2002). Several studies have addressed how regulation affects adoption of innovation in different industries (Dewick and Miozzo, 2002; Jaffe and Stavins, 1995; Sanchez and Post, 1998; Gruber and Verboven, 2001; Snyder et al., 2003; Wallsten, 2005; Sheppard et al., 2006). The pharmaceutical industry, however, is one of the most heavily regulated industries and provides a perfect test bed to assess how regulation affects adoption of innovation.

Pharmaceuticals deserve specific attention because consumption is channelled through an agency relationship and reimbursement is carried out by third party payers, which limits financial responsibility on the demand side leading to price insensitivity

and moral hazard in consumption. The industry significantly depends on monopoly rights granted by patents to recoup costly R&D outlays and maintain sustainability of future investments[1]. Such monopolistic power, however, allows pricing above marginal costs, which has historically focused regulators' attention on pharmaceutical prices as a major means of cost-containment.

Access to essential medicines is also increasingly recognized as a core part of the international right to health (Thomas, 2006). Given the global nature of pharmaceuticals and the reliance of the industry on returns to R&D, speedy and simultaneous introduction across markets would maximize commercial success. Pricing and reimbursement (P&R) regulations post-launch and the dependence of prices across markets create a tension between the aims of regulating prices and delaying adoption of pharmaceutical innovation, thus jeopardizing access to health enhancing pharmaceutical technologies (Danzon et al., 2005; Danzon and Epstein, 2008).

This paper will test the hypothesis that regulation has a significantly negative effect on the speed of new molecule adoption in markets that apply these regulations and investigate the ramifications of price linkages across individual markets created by external reference pricing and parallel trade. Drawing upon duration modelling applied to IMS (Intercontinental Medical Services) data we estimate the impact of regulation, identified by expected launch prices, on the probability of new molecule launch across the main OECD markets during 1999-2008 controlling for market structure, firm and molecule heterogeneity. We also further examine a sub-set of markets, within the EU, to assess whether firms employ strategic pricing behaviour.

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[1] R&D investments are estimated to be on the order of $800 million, with a range of $500 million to $2,000 million depending on the therapy or the developing firm (Adams and Brantner, 2006; Dimasi et al., 2003; Dimasi, 2002).

The rest of the paper is structured as follows: Section 2 discusses prior evidence from the literature; Section 3 describes the methods; Section 4 presents empirical results, and finally Section 5 discusses main findings of the paper.

2   BARRIERS TO ENTRY AND KEY DRIVERS OF ADOPTION

Lags in the adoption of pharmaceutical innovation can have different components in different countries, depending on specific local regulations. Several studies in the literature have addressed delays due to the review process (Dranove and Meltzer, 1994; Thomas et al., 1998; Carpenter et al., 2003; Carpenter and Turenne, 2004; Bolten and Degregorio, 2002), while more recent studies have emphasized price controls and variations in reimbursement schemes (Danzon et al., 2005; Danzon and Epstein, 2005; Danzon and Epstein, 2008; Lanjouw, 2005). In most OECD countries, firms face additional delays due to pricing and reimbursement approval. These controls not only affect the local commercial demand factors but also increase the interdependency across international markets due to knock-on effects of external reference pricing and parallel exports.

2.1   Identification of Regulation
Treatment Dummies for Price Controls

Two categories of studies exist with respect to how regulation is identified. The first category uses treatment dummies for price control at the time of launch (Lanjouw, 2005; Heuer et al., 2007; Kyle, 2007). Lanjouw (2005) includes treatment dummies for the stringency of price control to measure the impact of limited price control versus extensive price control in high-income and low-middle income countries. Heuer, Mejer et al. (2007) control for direct price regulation (international price comparisons, therapeutic value/cost-effectiveness, pharmaceutical contribution to the

4

economy) and indirect price regulation (profit control, reference pricing) in a probit analysis to test how different P&R schemes affect the probability of launch for new chemical entities approved by the centralized EMEA procedure within the former EU15 during 1995-2004. Kyle (2007) estimates a discrete-time survival model using data in 28 countries over 1980-2000 using price ranks and regulation dummies, such as prescription budgets, reference pricing, price freezes and controls. Studies in this first category identify a significant effect of price controls on the probability of launch. Countries with the highest probability of launch impose the lowest regulation on prices and indirect price controls do not affect launch delays significantly for on-patent drugs (Heuer et al., 2007). Kyle (2007) observes that launch in a price-controlled country significantly reduces the likelihood of introducing products in additional markets.

Expected Launch Prices

Treatment dummies and static price ranks control for regulation only roughly and potentially inaccurately given the dynamic and multidimensional nature of regulation. Price ranks may be highly heterogeneous with respect to therapeutic subgroups or across time. In addition, treatment dummies frequently exhibit multi-collinearity with country effects. There is a preliminary body of literature which has incorporated product-specific data on actual prices to identify the impact of regulation empirically (Danzon and Epstein, 2008; Danzon et al., 2005).

These studies differ broadly in their methodological approach and the mix of products and markets included in the analysis. Danzon, Wang et al (2005) proxy for expected price by the lagged average price per standard unit (SU)[2] for the therapeutic class

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2 IMS standard unit is the smallest dose for each form, for example, one tablet, one capsule, or 5 ml of liquid

(ATC3) in quarters 3 and 4 prior to the first global launch, whereas the other two studies use the average competitor prices in ATC4 prior to local launch. Danzon, Wang et al. (2005) use the continuous time Cox proportional hazard (PH) model whereas the later study uses discrete-time implementation of the PH model by complementary log log regression.

Findings from the second category suggest that the hazard of launch is positively related to expected price. In addition to regulatory market barriers, late entry may be due to strategic firm behaviour to avoid knock-on effects of price spillovers due to reference pricing and parallel trade. Overall, market size has a less robust effect on likelihood of launch. Danzon, Wang et al. (2005) identify a significant market size effect, whereas Danzon and Esptein (2008) conclude total volume of drugs in a therapeutic subgroup is not a significant factor. Similarly, evidence regarding home advantage in terms of quicker launch for firms headquartered in the destination market is more controversial. Danzon, Wang et al (2005) and Kyle (2007) identify a clear home advantage, while Danzon and Epstein (2008) conclude launch is faster only in certain regulated markets with strong pharmaceutical industries and industrial policies that support local firms, e.g. France, Italy, Spain.

This paper aims to address some of the methodological shortcomings of previous studies and provide additional evidence using a different drug mix and a more up-to-date analysis period. We prefer to use duration modelling to the probit model used by Heuer, Mejer et al. (2007) because of information loss induced by defining success as local launch within 8 months of first global launch. Also, we aim to control for drug and firm level heterogeneity to avoid omitted variable bias. In contrast to the approach followed by Kyle (2007), we consider only the first indication of molecules in each market as new indications face lower barriers and costs to entry both pre- and post-

authorization. Price negotiations for add-on indications may be quicker due to familiarity with the molecule. This approach also avoids attenuation in standard errors due to the potential correlation in errors for different indications of a given molecule-country pair.

3   METHODS

3.1   Data

The IMS data used in this study covers quarterly USD ($) and SU sales of new molecules in 13 different ATC1 therapeutic categories during 1999 Q1 – 2008 Q3. The dataset comprises 20 countries which represent the major pharmaceutical markets in the OECD (except for South Africa)[3]. Each product is identified by the molecule name, IMS generic classification, global and local launch dates, therapeutic class (ATC4), and breakdown of sales by the distribution channel (retail versus hospital). Spain, Turkey, Belgium, Greece, Portugal, Spain, South Africa have only retail channel data[4]; for Sweden retail and hospital sales are combined. The ex-manufacturer price level for molecules is calculated by dividing the ex-manufacturer USD sales of the molecule by sales volume in SU. This essentially assumes for each molecule a volume weighted average price across all products with the same active ingredient. We consider only ex-manufacturer price levels and ignore margin controls and marketing discounts along the distribution chain.

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[3] The country set in alphabetical order is: Australia, Austria, Belgium, Canada, Finland, France, Germany, Greece, Italy, Japan, Netherlands, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey, the UK and US
[4] Launch in these countries therefore represents launch in the retail sector.

OECD statistical extracts were used to get additional data for GDP per capita[5]. Sales data was deflated using GDP deflators from the International Monetary Fund World Economic Outlook Database 2008[6]. Observations with negative sales representing products returned to the manufacturer after withdrawal from the market, and which accounted for about 5% of the total number of observations, were dropped.

The global launch date of a given molecule defines the onset of risk for subsequent launches in other markets. The launch dates are recorded monthly. Molecule-country pairs comprise the unit of analysis. Failure time for molecule j-country k pair is defined as the difference between the global launch date of molecule j and the local launch date of molecule j in country k. The molecule set is restricted to molecules that have launched in at least ten markets, which is a more stringent measure of global importance compared to prior studies. Prior studies at best consider either molecules that have launched in the US or UK. Due to the different dynamics after the establishment of a single European market in 1993, the molecule set is further restricted to include molecules that first launched post-1993.

The dataset is first brought into a suitable format to do non-parametric survival analysis and is then expanded to define monthly time intervals following the global launch date until the local failure (launch or censoring) to account for the interval-censored nature of the launch timing data. Quarterly average price is assumed for each month in the same quarter.

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[5] Available at http://stats.oecd.org/index.aspx
[6] Real sales figures were calculated as : Real Sales = Nominal Sales*100/GDP deflator

3.2   Model

Entry of a molecule in a given country can be considered as a binary-outcome model defined as unity if entry occurs at time t and zero otherwise. Letting Π_{jkt} represent the discounted post-entry profits for molecule j in country k if entry occurs at time t, the entry decision d_{jkt} is defined as:

$$d_{jkt} = \begin{cases} 1 & \text{if } \Pi_{jkt} > 0 \text{ and } d_{jkn} = 0, \text{for all } n \leq t\text{-}1 \\ 0 & \text{otherwise} \end{cases}$$

Π_{jkt} is composed of the discounted future profit stream, net of any costs of entry. Π_{jkt} is a latent variable which is not observed directly; only the launch decision d_{jkt} is observed. In an isolated market, the discounted future profit stream ignoring marginal costs is $\sum_{t=1}^{LT_{jk}} \delta^t \{P_{jkt}Q_{jkt}\} - E_{ijt}$, where P is the expected local price; Q is the expected market size for molecule j in country k; E is the fixed cost of entry; LT is the expected life-time of the molecule in the destination market and δ is the discount factor. Companies would like to launch as quickly as possible for two reasons: raising prices post-entry is difficult either due to regulation or competition and a longer protection period avoids generic competition's effect on prices and market shares. However, in interdependent markets such as the EU, there would be an additional loss term (L) due to external referencing or parallel trade between the destination market k and markets r that have already adopted the technology and reference prices in market k (Danzon and Epstein, 2008). The profit equation would then become $\sum_{t=1}^{LT_{jk}} \delta^t \left\{ P_{jkt}Q_{jkt} - \sum_{r \neq k} L_{jkrt} \right\} - E_{ijt}$, which shows the international character of pricing and launch strategies of new pharmaceutical products. The size of

the loss *L* would depend on prices and market sizes in countries *k* and *r*. Companies could forego launch in small sized and low-priced markets to preserve profits in bigger markets with higher prices.

The expected price *P* is also a function of price controls and the degree of competition in the therapeutic subgroup. One of the key product attributes of on-patent pharmaceutical technologies is quality. A quality advantage (addressing unmet needs or offering improved effectiveness and/or fewer side effects) potentially results in a price mark-up. Even in price controlled markets, especially if pharmaceutical sector plays an important role in the economy, price mark-ups are given as an incentive to stimulate pharmaceutical innovation.

The expected market size *Q* depends on total sales in the therapeutic category, which is a function of the population and the prevalence rate of the condition as well as demand-side controls that may define limits on *Q* through price-volume agreements. Depending on economies of scale, firms can invest in promotional efforts to influence prescribing decisions of physicians to increase sales volume.

Defining row vectors of regulation, competition, molecule, firm characteristics respectively as $\mathbf{R}, \mathbf{C}, \mathbf{M}$, and $\mathbf{F}$, the additive reduced-form profit function can be specified as:

$$\Pi_{jkt} = \mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} = \mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt},$$

where $\boldsymbol{\beta}_R$, $\boldsymbol{\beta}_C$, $\boldsymbol{\beta}_M$, and $\boldsymbol{\beta}_F$ represent corresponding column vectors of parameters to be estimated. γ_t is a function of *t*, time since global launch of molecule *j*. Given that launch has not occurred up to interval *t*, the conditional probability of launch during interval *t*, i.e. the interval hazard rate is:

$$\Pr(d_{jkt} = 1 \mid T_{jk} \geq t) = h_{jk}(t) = \Pr(\mathbf{R}_{jkt}\boldsymbol{\beta}_R + \mathbf{C}_{jkt}\boldsymbol{\beta}_C + \mathbf{M}_{jk|t}\boldsymbol{\beta}_M + \mathbf{F}_{jk|t}\boldsymbol{\beta}_F + \gamma_t + u_{jkt} > 0)$$

$$h_{jk}(t) = \Pr(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t + u_{jkt} > 0)$$

$$h_{jk}(t) = \Pr(u_{jkt} > -\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t) = 1 - F(-\mathbf{z}_{jkt}\boldsymbol{\beta} - \gamma_t) = F(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t)$$

where $F(.)$ is the cumulative distribution function of u and T_{jk} is the launch time of

molecule j in country k.

For the cloglog model $F(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t) = 1 - \exp\{-\exp(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t)\}$ and thus the hazard

rate can be defined as:

$$h_{jk}(t) = 1 - \exp(-\exp(\mathbf{z}_{jkt}\boldsymbol{\beta} + \gamma_t)).$$

The marginal effect of h with respect to $\mathbf{z}_j$ is given by:

$$\frac{\partial h}{\partial z_j} = \exp\{-\exp(\mathbf{z}_j\boldsymbol{\beta} + \gamma_t)\}\exp(\mathbf{z}_j\boldsymbol{\beta} + \gamma_t)\beta_j,$$ which implies that the marginal effect

has the same sign as the parameter estimate. The empirical analysis assumes two

different duration specifications: i) a parametric specification for $\gamma_t = \gamma_1 t + \gamma_2 t^2$; and

ii) a semi-parametric specification that includes dummies for each year following

global launch.

We classify variables that define the decision of entry broadly as external

environment and internal environment factors. External environment variables are

those defined outside the boundaries of the firm, whereas internal environment

variables are defined by firm strategies and internal managerial decisions. This

approach brings together the conceptual framework used in the marketing and

strategy literature with the findings from the industrial organization (IO) literature

regarding the drivers of market entry (Wong, 2002; Chryssochoidis and Wong, 1998).

A list of descriptive statistics for the variables is provided in the Appendix (Table A.I). External environment variables include regulation, market environment and competition, whereas internal environment is defined by variables that control for firm and molecule heterogeneity.

4   RESULTS

Table I presents the base case estimates of marginal effects estimated by complementary log log regression for molecules that first launched globally after 1993. The results are presented both with respect to quadratic duration specification with a second-order polynomial in time since global launch, and a semi-parametric specification.

4.1   Regulation and Market Size

The net effect of regulation is defined by expected launch prices as static treatment dummies would not capture the complexity in pricing mechanisms and the variation over time, across therapeutic categories, firms and countries. Expected prices are calculated as the average non-generic competitor prices in the same ATC4 lagged by one quarter. Generic products are excluded from average price calculations since inclusions of generics in expected price calculation would underestimate expected prices in countries with loose price regulation but strong generic penetration and would result in imprecise coefficient estimates. Expected market size for a new molecule is defined as quarterly lagged total SU sales within the molecule's ATC4 in individual markets. ATC4 is used to define the potential market since competition and substitution effects are strongest at the ATC4 level.

Regulation is seen to have a significant and robust effect on timing of launch. In all regression specifications the estimates for price and volume are highly significant (p= 0.001). A unit increase in the log expected launch price and the log of expected market size increases the probability of launch by 0.003 and 0.002 respectively (see Table I). This is close in value to 0.0053, the marginal effect of expected price for superior molecules in Danzon and Epstein (2008). Standard error estimates of expected price are slightly lower because we cluster by molecule-country rather than by molecule since autocorrelation may exist between consecutive error terms of a molecule-country pair. The effect of log GDP per capita ($) is positive but not significant, and therefore excluded in the second specification.

[TABLE I here]

4.2 Competition

Competition, proxied by the Herfindahl-Hirschman Index (I_{HH}), has a significant effect on the likelihood of launch. It is a stylized fact in the IO literature that high concentration reduces the equilibrium level of entry in several industries; however, no prior study has tested this in the pharmaceutical sector by specifically considering the impact of molecule concentration on the hazard of launch. I_{HH} is defined

as $I_{HH} = \sum_{i=1}^{N} \left(s_i^2 \right)$, where s_i is the market share of molecule i and N is the number of

molecules in the therapeutic subgroup ATC4. Subgroup concentration, as expected, constitutes a barrier to entry. A unit increase in the log of I_{HH} reduces the hazard rate by 0.005 in the quadratic specification and by 0.004 in the semi-parametric one, which implies the more competitive the subgroup, the higher is the likelihood of quick launch.

We carry out robustness checks by controlling for the number of substitute molecules and investigate whether generic competition is significant (Table A.II). We consider only quadratic duration specification for robustness checks as base case estimates suggest the fit of quadratic and semi-parametric specifications are comparable. Intermolecular competition is found to be more influential on the decision of entry compared to the extent of generic competition proxied by the number of substitute molecules with generic competition. Consistent with findings of Kyle (2007) the number of competitor molecules in the same ATC4 significantly increases the hazard of launch, while the number of molecules with generic competition has no significant effect on the launch decision of new molecules.

4.3 Firm Characteristics

Firm effects play a key role in the strategic entry decisions within the pharmaceutical sector (Kyle, 2006; Kyle, 2007; Scott Morton, 1999). Large-firm advantage in pharmaceutical regulation has been suggested due to familiarity of the regulator with large firms and regulators favouring early entrants (Carpenter and Turenne, 2004). Similarly, scale effects suggest an advantage in promotional activities to influence physician prescribing levels. Larger firms have better prospects of entry through licensing in foreign markets and cost advantages to overcome costs of entry that constitute a significant barrier to entry in the pharmaceutical sector.

Economies of scope imply potentials for R&D and knowledge spillovers across different drugs. Learning effects through multiple launches in a given market can enable firms to come up with more efficient launch strategies. Similarly, clinical trial data obtained in one country can generally be used for launch in further markets.

14

The base case analysis controls for firm effects by log number of countries the firm has launched in. Firm heterogeneity is found to be highly significant; a unit increase in the log number of countries a firm has launched in (equivalent to multiplying geographical reach by 2.72) increases the hazard of launch by 0.011, which is close to the 0.009 estimate of Kyle (2007). Firms with a wider global reach have a strategic advantage compared to more locally oriented firms.

Robustness checks were carried out by controlling for log firm sales in 2007, total and local numbers of firm molecules firms have launched to control for economies of scope (Table A.III). All scale and scope variables are robustly positive and significant. Portfolio diversity (number of prior molecules launched) is associated with quicker launch, which is in contrast to findings of Kyle (2007). We find no evidence of advantage through domestic launch.

4.4 Molecule Characteristics

Therapeutic quality is the main factor that defines product differentiation and strategic positioning of a new pharmaceutical technology. In addition, therapeutic importance of molecules affects the timing of P&R decisions as it is a key criterion in many countries. Products that offer therapeutic novelty or public health advantages with significant implications for health budgets may be eligible for a fast track approval and receive a price mark-up compared to existing products.

In the base case analysis presented in Table I molecule's global sales in 2007 are used to control for molecule characteristics since therapeutic importance and commercial success are highly positively correlated. A unit increase in the log molecule sales globally increases the hazard of launch by 0.004. In the robustness checks, we proxied for therapeutic importance using the total number of markets in which a molecule has

launched, i.e. global extent of launch (Table A.IV). The extent of global reach, as expected, was found to have a significantly positive effect on the probability of launch with a marginal effect of 0.059.

4.5   Time Effects

Time may affect regression estimates in several ways. First, macroeconomic trends in the sector may have an impact on price levels. This is accounted for by including dummies for each calendar year in all regressions. Second, time captures information about the relative innovativeness of new molecules. When a new molecule is about to launch, it represents incremental (or breakthrough) innovation compared to the molecules in its therapeutic subclass. The longer the time lapse from global launch, the higher is the probability that new competitors will enter to compete against the molecule lowering its comparative therapeutic advantage.

The impact of time elapsed since first global launch is captured by interacting both expected price and volume with time since global launch. A dummy variable (First Launch Before 1999) is included to test if the hazard of launch is statistically different for molecules that launched globally after 1999 compared to the ones that launched first globally during [1993, 1999). Remember that the set of molecules was restricted to the ones that first launched after the establishment of the EU in 19993 and that all the failures, i.e. local launches, are post-1999. Therefore, molecules with first global launch pre-1999 are left-truncated. Left-truncation is dealt with by omitting the subject from all binary outcome analyses during the truncation period since the subject could not have failed during that period (Cleves et al., 2008).

Time interactions of price and volume are significantly negative, which suggests that the impact of price and volume decays over time following the global launch of the

molecule. Molecules that launched first before 1999 have a significantly lower hazard rate compared to molecules that launched after 1999; the marginal effect is in the range of -0.018 to -0.014 depending on the model specification (see Table I).

Parameter estimates of t and t^2 suggest concave duration dependence, while the hazard of launch initially increases and then decreases, which is in contrast to prior findings of Danzon and Epstein (2008) who observed that hazards first decrease then increase with time since global launch. This might be because the molecules in this analysis are more recent, and hence potentially more innovative, and have a higher extent of global reach overall (all molecules have launched in at least 10 markets).

Thus to summarise, *ceteris paribus*, price reductions and low competition increases time-to-entry, while larger market size, higher therapeutic importance and the greater the number of markets a firm operates in reduces time-to-entry. Products that first launched globally since 1999 appear to have been adopted internationally more quickly than those in the period 1993 to 1999.

4.6 EU Subsample Analysis

Finally, the country set was restricted to EU countries to check for the impact of price interdependency across markets (Table A.V). There is strong evidence that external referencing slows down adoption of innovation. Launch in a high-priced EU market increases the hazard by 0.042 compared to launch in a lower priced EU-market for molecules. This effect increases to 0.051 for molecules that first launched after 1999, suggesting an increase in the strategic importance of price in the timing of entry.

From a strategic perspective, firms may risk the loss of competitive innovative edge as delays increase the chance of facing further competition later in time (Kyle and National Bureau of Economic, 2007). This suggests a second firm strategy, which

involves pursuing convergence of prices in the EU market following launch to avoid knock-on effects due to parallel trade and external referencing, even if at the expense of foregoing some short-term local profits in some markets. We test for this strategy, by controlling for the extent of deviation between expected local price and the average EU price for the launching molecule (Table A.VI). The absolute difference between the local expected price and average EU price significantly decreases the hazard of launch; the sign of this difference remains insignificant. Launch and pricing strategies are multi-market optimization decisions; the trend to drive prices closer across different geographies may potentially reduce global prices.

5 DISCUSSION

This paper aimed to investigate how regulation, in particular price regulation, affects the adoption of pharmaceutical products across the main OECD markets during 1999-2008. We empirically show evidence of relative delays in the adoption of a potentially global set of molecules have diffused to more than 10 markets in the OECD, controlling for external and internal firm environment.

Results suggest a statistically significant and robust effect of price on timing of launch. High ex-ante price expectations increase the speed of pharmaceutical adoption internationally. Hence, we can conclude that regulations that create price linkages across markets may thus result in delayed access to pharmaceutical innovation because of profit implications in subsequent markets and strategic firm behaviour to avoid profit loss. Our results would indirectly support this argument, but also indicate a significant and robust market size effect that increases the likelihood of new pharmaceutical adoption as market size increases.

We observe significant firm and molecule heterogeneity in the speed of launch. In particular, firm economies of scale and molecule's therapeutic importance grant substantial advantages for timely roll-out internationally. Contrary to what the prior literature suggests, we find no significant advantage to domestic launch. Higher therapeutic subgroup concentration constitutes a market barrier to timely adoption of new technologies, which confirms the importance of policies directed at fostering competition in the pharmaceutical sector.

Findings in this paper suggest several policy implications. First, price regulations slow down pharmaceutical adoption on a global scale and may impose welfare losses, particularly when the innovations that are delayed are cost-effective from a societal perspective. The new value based pricing system proposed by the UK government could have significant knock-on effects in countries that reference the UK, which make up approximately 25% of the global market according to the Office of Fair Trading (O.F.T, 2007; Hirschler, 2010).

Delays in adoption reduce the net present value of R&D investments by delaying cash flows and shortening the exclusivity period, which reduces future R&D and innovation (Giaccotto et al., 2005). Therefore, although price controls may increase static efficiency in the short term by driving prices and marginal costs closer, they could also result in potential losses in dynamic efficiency due to reduced incentives to entry.

From a public health perspective, lack of access to new drugs may lead to compromises in health outcomes (Schoffski, 2002), shift volume to older molecules of lower therapeutic value (Danzon and Ketcham, 2004) and compromise the quality of health care (Kessler, 2004; Wertheimer and Santella, 2004). Innovative

medications offer economic benefits by avoiding expenditures on other forms of medical care (such as hospitalization) as well as reducing missed work days (Hassett, 2004; Lichtenberg, 1996; Lichtenberg, 2003; Lichtenberg, 2005). Again, in a wider context, the assessment of short-term efficiency gains brought about through price regulation should be weighed against potential long-term implications on public health outcomes and dynamic efficiency. This study has merely provided evidence on the impact of price on time-to-market launch, and the continuation of debate over static and dynamic efficiency gains falls outside the scope of this paper.

Second, our analysis confirms that extensive price controls could reduce incentives to entry and result in a less competitive environment to stimulate further innovation. Third, local controls can affect firms' launch decisions in foreign markets and impose welfare losses, especially in lower-priced markets. Finally, due to scale advantages in international roll-out strategies, price controls may increase incentives for mergers and acquisitions, further increasing concentration levels and barriers to entry.

This paper contributes to the literature in several ways. First, we exploit the variation both over time and molecule-country pairs. The robustness of the results has been assessed by different duration specifications and alternative proxies for risk factors. Second, the dataset is more comprehensive and up-to-date than comparable empirical studies in the literature. Third, the analysis makes use of reliable price and volume information. The price effect is calculated controlling for firm and molecule heterogeneity that could bias the estimates if omitted. Finally, the analysis is carried out for potentially global molecules, which ensures findings are relevant from an international perspective.

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TABLES

Table I. Marginal Effects for Base Case Regression Results

Molecules with Global Launch post-1993	Marginal Effects in Cloglog (quadratic in t)		Marginal Effects in Cloglog (semi-parametric)	
	1	2	1	2
Log Lagged Average Non-Generic Price/SU in Ctry-ATC4	0.003*** [0.0007]	0.003*** [0.0007]	0.003*** [0.0006]	0.003*** [0.0007]
Log Lagged Total SU in Ctry-ATC4	0.002*** [0.0005]	0.002*** [0.0005]	0.002*** [0.0005]	0.002*** [0.0005]
Log GDP per capita		0.017 [0.0241]		0.024 [0.0240]
Log Molecule Concentration in Ctry-ATC4 (IHH)	-0.005*** [0.0010]	-0.005*** [0.0010]	-0.004*** [0.0010]	-0.004*** [0.0010]
Log Number of Countries Firm has Launched in	0.011*** [0.0019]	0.011*** [0.0021]	0.010*** [0.0018]	0.011*** [0.0021]
Log Global Molecule Sales in 2007	0.004*** [0.0005]	0.004*** [0.0006]	0.004*** [0.0005]	0.004*** [0.0005]
Log Lagged Average Non-Generic Price/SU in Ctry-ATC4*ln(t)	-0.001** [0.0003]	-0.001** [0.0003]	-0.001*** [0.0003]	-0.001*** [0.0003]
Log Lagged Total SU in Ctry-ATC4*ln(t)	-0.001*** [0.0002]	-0.001*** [0.0002]	-0.001*** [0.0002]	-0.001*** [0.0002]
First global launch before 1999	-0.018*** [0.0032]	-0.020*** [0.0033]	-0.014*** [0.0031]	-0.016*** [0.0032]
Years since global launch (t)	0.012*** [0.0018]	0.012*** [0.0019]		
Years since global launch squared (t^2)	-0.001*** [0.0002]	-0.001*** [0.0002]		
AUSTRIA	0.043*** [0.0096]	0.043*** [0.0096]	0.042*** [0.0093]	0.042*** [0.0093]
BELGIUM	0.005 [0.0056]	0.005 [0.0058]	0.003 [0.0052]	0.003 [0.0054]
CANADA	0.01 [0.0062]	0.009 [0.0062]	0.009 [0.0058]	0.008 [0.0059]
FINLAND	0.041*** [0.0094]	0.044*** [0.0104]	0.039*** [0.0091]	0.043*** [0.0102]
FRANCE	0.001 [0.0054]	0.003 [0.0062]	0 [0.0051]	0.003 [0.0060]
GERMANY	0.059*** [0.0121]	0.062*** [0.0130]	0.056*** [0.0116]	0.060*** [0.0126]
GREECE	0.014* [0.0065]	0.021 [0.0133]	0.011 [0.0060]	0.022 [0.0133]

ITALY	0.006 [0.0052]	0.009 [0.0067]	0.005 [0.0049]	0.008 [0.0064]
JAPAN	-0.017*** [0.0036]	-0.016*** [0.0042]	-0.015*** [0.0035]	-0.014*** [0.0041]
NETHERLANDS	0.075*** [0.0155]	0.072*** [0.0156]	0.072*** [0.0151]	0.070*** [0.0151]
POLAND	0.004 [0.0053]	0.024 [0.0338]	0.003 [0.0049]	0.033 [0.0376]
PORTUGAL	0.005 [0.0068]	0.015 [0.0174]	0.004 [0.0062]	0.018 [0.0181]
SAFRICA	0.003 [0.0058]		0.001 [0.0053]	
SPAIN	0.009 [0.0062]	0.014 [0.0096]	0.007 [0.0058]	0.014 [0.0094]
SWEDEN	0.057*** [0.0126]	0.059*** [0.0128]	0.057*** [0.0124]	0.059*** [0.0126]
SWITZERLAND	0.022** [0.0079]	0.020* [0.0085]	0.020** [0.0074]	0.016* [0.0079]
TURKEY	-0.005 [0.0045]	0.017 [0.0386]	-0.006 [0.0042]	0.029 [0.0451]
UK	0.048*** [0.0101]	0.049*** [0.0104]	0.046*** [0.0099]	0.048*** [0.0103]
US	0.083*** [0.0205]	0.074** [0.0234]	0.081*** [0.0196]	0.069** [0.0220]
Calendar Year Dummies [a]	yes	yes	yes	yes
ATC1 Dummies	yes	yes	yes	yes
Post Global Launch Yearly Interval Dummies [b]	no	no	yes	yes
Number of observations	54594	51132	54594	51132
Log Likelihood	-10131.277	-9619.788	-10076.972	-9568.201
chi2	1132.456	1077.675	25042.756	1.99E+09
p	0.000	0.000	0.000	0.000
Akaike's Information Criterion	20364.554	19341.577	20279.943	19262.401
Bayesian information criterion	20818.846	19792.527	20841.127	19819.458

Note: *p<0.05, **p < 0.01, ***p<0.001.

   Standard errors (in brackets) clustered at molecule-country level

   [a] Dummies available upon request

   [b] For semi-parametric duration specification

APPENDIX

Table A.I. Variable Definitions and Descriptive Statistics for the Data used in Survival Analysis

External Environment	Variable Name	Descriptive Statistics			
Regulatory Environment		*Mean*	*Std Dev*	*Min*	*Max*
Expected Price	Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4[a]	0.43	2.5	-10.161	8.16
Relative Price	High Price EU	0.29	0.46	0	1
Price Setting	External Referencing	0.83	0.37	0	1
Market Environment					
Expected Market Size	Log Lagged Total SU in Ctry-ATC4	7.03	3.27	-6.91	14.7
GDP per capita	Log GDP per capita ($)	10.13	0.39	8.99	10.74
Competitive Environment					
Market Concentration	Log Molecule Concentration in Ctry-ATC4(IHH)	10.058	1.158	5.72	15.94
Intermolecular Competition	Log Number of Molecules in Ctry-ATC4	1.401	1.795	-4.61	5.42
Generic Competition	No. of Molecules with Generic Comp in Ctry-ATC4	0.647	2.253	-4.61	5.29
Internal Environment					
Firm Characteristics					
Economies of Scope	Log Firm Sales (global) in 2007	14.9	3.21	-4.56	17.45
	Log Number of Countries Firm has Launched in	2.45	1.03	0	3
Economies of Scale	Log Firm's Total Number of Molecules	5.49	1.47	0.00	7.22
	Log Local Firm Experience (number of molecules launched)	4.09	1.33	0	6.65
Location of Firm Headquarters	Domestic Launch	0.11	0.31	0	1
Molecule Characteristics					
Therapeutic/Commercial Importance	Log Global Molecule Sales in 2007	11.038	2.194	-4.88	16.26
	Log Molecule's Global Reach (total markets launched in)	2.713	0.211	2.3	3
Period of Global Launch (old vs new)	First Launch Before 1999	0.67	0.47	0	1

Note: [a] All lags are by one quarter.

Table A.II Robustness Check: Market Structure and Competition

Variables	Marginal Effects in Cloglog (quadratic in t)			
	1	2	3	4
Log Lagged Avg Price/SU in ATC4	0.003*** [0.0007]	0.004*** [0.0009]	0.003*** [0.0007]	0.004*** [0.0007]
Log Lagged Total SU in Ctry-ATC4	0.002*** [0.0005]	0.003*** [0.0006]	0 [0.0005]	0.001 [0.0005]
Log Molecule Concentration in Ctry-atc4 (IHH)	-0.003** [0.0010]	-0.002 [0.0011]	0 [0.0011]	0 [0.0010]
Log Number of Molecules with Generic Comp in Ctry-ATC4		0 [0.0005]		
Log Number of Molecules in Ctry-ATC4			0.012*** [0.0014]	0.012*** [0.0014]
Log Lagged Avg Price/SU * ln(t)				-0.001** [0.0003]
Log Lagged Total SU * ln(t)				-0.001*** [0.0002]
First Launch Before 1999				-0.014*** [0.0034]
Years since global launch (t)	0.003** [0.0012]	0.003** [0.0012]	0.003** [0.0012]	0.011*** [0.0018]
Years since global launch squared (t^2)	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0002]
Country Dummies	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes
Number of Observations	54721	38098	54721	54721
LogLikelihood	-10290.07	-6731.46	-10246.68	-10225.81
Akaike's Info Crit	20672.15	13556.92	20587.35	20551.62
Bayesian Info Crit	21082.01	13958.68	21006.12	20997.12

Note: *p<0.05, **p < 0.01, ***p<0.001.
Standard errors clustered at molecule-country level (standard errors in brackets).
Non-exponentiated parameter estimates reported

Table A.III Robustness Check: Firm Effects

Variables	Marginal Effects in Cloglog (quadratic in t)			
	1	2	3	4
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.003*** [0.0004]	0.003*** [0.0004]	0.002*** [0.0004]	0.003*** [0.0004]
Log Firm Sales (global) in 2007	0.004*** [0.0005]			0.005*** [0.0005]
Log Number of Countries Firm has Launched in		0.009*** [0.0017]		
Log Local Firm Experience (number of molecules launched)		0.003*** [0.0006]		
Log Firm's Total Number of Molecules			0.003*** [0.0006]	
Domestic Launch			-0.002 [0.0035]	0.009 [0.0047]
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4 * ln(t)				-0.001** [0.0003]
Log Lagged Total SU in Ctry-ATC4 * ln(t)				-0.001*** [0.0002]
First Launch Before 1999				-0.013*** [0.0028]
Years since global launch (t)	0.005*** [0.0011]	0.005*** [0.0011]	0.004*** [0.0011]	0.012*** [0.0017]
Years since global launch squared (t2)	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]
Country Dummies	Yes	Yes	Yes	Yes
ATC1 Dummies	Yes	Yes	Yes	Yes
Calendar Year Dummies	Yes	Yes	Yes	Yes
Number of Observations	58521	58530	58530	58521
LogLikelihood	-10487.9	-10502.04	-10526.97	-10463.85
Akaike's Info Crit	21067.79	21098.08	21147.94	21027.70
Bayesian Info Crit	21480.74	21520.01	21569.87	21476.56

Note: *$p<0.05$, **$p < 0.01$, ***$p<0.001$. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported

Table A.IV Robustness Check: Molecule Characteristics

	Marginal Effects in Cloglog (quadratic in t)		
	1	2	4
Log Lagged Price/SU	0.003*** [0.0006]	0.003*** [0.0006]	0.003*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.002*** [0.0004]	0.002*** [0.0004]	0.002*** [0.0004]
Log Global Molecule Sales	0.003*** [0.0005]		
Log Molecule's Global Reach		0.059*** [0.0059]	0.059*** [0.0058]
Log Lagged Avg Price/SU * ln(t)			-0.001** [0.0003]
Log Lagged Total SU * ln(t)			-0.001*** [0.0002]
First Launch Before 1999			-0.010*** [0.0028]
Years since global launch (t)	0.004*** [0.0011]	0.004*** [0.0011]	0.011*** [0.0017]
Years since global launch squared	-0.001*** [0.0001]	-0.001*** [0.0001]	-0.001*** [0.0001]
Number of Obs	58279	58530	58530
LogLikelihood	-10433	-10485	-10467
Akaike's Info Crit	20958	21061	21031
Bayesian Info Crit	21370	21474	21471

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported. Country, ATC1 and calendar-year dummies included

Table A.V Robustness Check: Regulation EU subsample

Variables	Marginal Effects by Cloglog (quadratic in t)		
	1	2	3 (post-99)
Log Lagged Avg Price/SU	0.004*** [0.0007]	0.004*** [0.0007]	0.005*** [0.0010]
Log Lagged Total SU	0.003*** [0.0005]	0.003*** [0.0005]	0.004*** [0.0007]
External Referencing	-0.030*** [0.008]		
High Price EU		0.042*** [0.008]	0.051*** [0.013]
Years since global launch (t)	0.007*** [0.0015]	0.007*** [0.0015]	0.026*** [0.0032]
Years since global launch squared (t^2)	-0.001*** [0.0002]	-0.001*** [0.0002]	-0.003*** [0.0006]
Number of Obs	39189	39189	23767
LogLikelihood	-7420.85	-7420.85	-4899.87
Akaike's Info Crit	14919.69	14919.69	9877.746
Bayesian Info Crit	15254.16	15254.16	10192.71

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported . Country, ATC1 and calendar-year dummies included

Table A.VI EU Subsample: Test for Expected Price Deviations from the Average Price of the Launching Molecule

Variable	Parameter Estimates by Cloglog (quadratic in t)	
	1	2
Log Lagged Avg Non-Generic Price/SU in Ctry-ATC4	0.083*** [0.02]	0.079*** [0.02]
Log Lagged Total SU in Ctry-ATC4	0.056*** [0.01]	0.055*** [0.01]
Absolute Difference btw Local Expected Price and Average EU Price (ΔP = Local Expected Price – Average EU Price)	-0.124* [0.06]	-0.141** [0.04]
Absolute ΔP * Sign(ΔP)	-0.031 [0.07]	
Sign(ΔP) [a]		-0.001 [0.06]
Years since global launch (t)	0.106** [0.04]	0.105** [0.04]
Years since global launch squared (t^2)	-0.018*** [0.00]	-0.018*** [0.00]
Country Dummies	Yes	Yes
ATC1 Dummies	Yes	Yes
Calendar Year Dummies	Yes	Yes
Number of Observations	27322	27322
LogLikelihood	-5624.5	-5624.58
Akaike's Info Criteria	11326.99	11327.16
Bayesian Info Criteria	11647.40	11647.56

Note: *p<0.05, **p < 0.01, ***p<0.001. Standard errors clustered at molecule-country level (standard errors in brackets). Non-exponentiated parameter estimates reported .
[a] Sign Defined to be 1 if $\Delta P \geq 0$ and 0 otherwise.