Joan Costa-Font, Alistair McGuire and Nebibe Varol

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Regulation Effects on the Adoption of New Medicines

Joan Costa-Font, Alistair McGuire and Nebibe Varol

London School of Economics and Political Science (LSE)

Contact: Dr Joan Costa-Font, London School of Economics, Houghton Street WC2A 2AE. London, UK. E-mail: j.costa-font@lse.ac.uk

Abstract

This paper analyses the impact of reimbursement regulation on launch times in the adoption of new medicines in a sample of OECD countries and a subsample of European countries. The latter also allows examination of price spillover effects, given that pharmaceutical product reimbursement regulation commonly benchmarks from prices in other countries. We empirically focus on the relative delays imposed by regulation on the adoption of a global set of molecules, which have diffused across more than 10 markets in the OECD over the period 1999-2008, controlling for various confounding effects. Through examining time to launch across a number of markets, and controlling for a number of confounding influences, we find that price and reimbursement regulations appear to delay the adoption of new pharmaceutical products. We also find the existence of interdependencies in pricing may have a further indirect effect of such regulation on launch times. Firm economies of scale, the therapeutic importance of specific product innovations and market size are found to counter the delaying impact of price and reimbursement regulation on new medicines adoption.

Keywords: pharmaceutical innovation, medicines adoption, regulation, duration analysis
JEL: I18

1 INTRODUCTION

The vast majority of the wealthy countries, as defined through membership of the Organisation for Economic Cooperation and Development (OECD), employ pricing and reimbursement (P&R) controls on pharmaceutical products to help contain health care costs and promote rational drug use. The entry of new pharmaceuticals products into a national market is directly affected by such country-specific regulations. The pursuit of such (static efficiency) policies might however conflict with dynamic efficiency objectives if price and reimbursement regulation deters the early adoption of innovative products. However, the empirical evidence regarding the impact of such regulation on the launch timing of pharmaceutical products is scarce.

This paper empirically examines the launch times of new medicines accounting for the effects of regulation within an environment of product competition. We address methodological shortcomings of previous studies (Danzon et al, 2005; Danzon and Esptein, 2008; Kyle 2006, 2007) and provide additional evidence on product launch times using a different drug mix and a more up-to-date analysis period that takes into account the existence of price externalities. We only consider the launch time of the first indication of molecules in each market as we anticipate that these new indications face higher barriers and costs to market entry. Given that patent protection is granted for new chemical entities (NCEs), essentially molecule entities, rather than products themselves, we believe that these first molecule entities represent innovation best.

Price negotiations for further products with similar NCEs are expected to be quicker due to familiarity with the molecule. This reliance on first molecule timings also avoids attenuation in standard errors due to potential correlation in errors for different indications of a given molecule-country pair. We use duration modelling to avoid information loss, while controlling explicitly for drug and firm level heterogeneity to avoid omitted variable bias. As well as adding to the small literature that has addressed similar questions, unlike previous research we also explore the effect of price linkages across individual markets as created by external reference pricing and parallel trade in the European Union, through a secondary analysis focussing on European markets alone. We do so by drawing on a unique dataset from the

Intercontinental Medical Services (IMS) that contains data from the main OECD markets during 1999-2008, a period during which important regulatory reforms have taken place.

Several studies have addressed how regulation affects adoption of innovative products 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). Arguably the unique regulatory nature of the pharmaceutical market provides a strong test to assess how regulation affects adoption of innovative products. In this sector products are initially subject to regulation with regards to their safety and subsequently with regards to their efficacy, where their clinical effects are assessed with respect to a placebo or the existing standard therapy. Finally, after marketing approval has been granted and given that most new pharmaceuticals are purchased by health insurers or other third party payers, (such as government funded health service providers), products may also be subject to price and reimbursement regulation based on product characteristics such as their similarity to existing product treatment effects and/or a judgment of their value for money in providing additional clinical benefit over existing products.

Such pricing and reimbursement regulation generally assumes that the costly R&D outlays spent on the development of new products be treated as a sunk cost. These R&D investments can be substantial and have been estimated to be of the order of $800 million per new marketed product, 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). Individual firms are granted patent protection providing a means of appropriating returns to R&D activity, and the associated sunk costs, through the creation of time-limited monopoly rights to suppliers. Generally, and specifically for the countries analysed in this study, patent protection is for 20-years, although this time is eroded in various ways – for example through the varying length of clinical trials to establish product quality, safety and efficacy and the rigour of the country specific reimbursement process.

Note also that these are not full monopoly rights as patent protection is defined over new chemical entities (NCEs), essentially molecule based compounds, not individual

products. Patent protection may be given to numerous similar NCEs, which may result in the establishment of highly substitutable products within a market; all of which may be considered to be of some innovative quality but nevertheless belong to the same therapeutic class of pharmaceutical.

The average time for granting of marketing approval over the period 1999-2003, according to the UK's Pharmaceutical Industry Competitive Task Force, was 13.7 months. Following marketing approval pricing and reimbursement regulation, based on formal guidance and accompanying negotiation begins. Given the global nature of the industry and the inter-relatedness of individual country markets, individual firms are conscious of the timing of launch across individual markets. Firms are particularly aware that smaller markets often price-reference to larger markets, thus establishment of appropriate price and reimbursement in any given market often impacts on the price obtained elsewhere. Moreover price differentials across countries, especially within the EU, may lead to so-called parallel imports, where cheaper drugs are imported into higher priced markets. Price and reimbursement regulation therefore affects product launch timings directly, but also indirectly through the resulting firm strategies used to maximise global sales in major markets. If firms can maximise price in any given market, then subsequent launches in other reference markets can build on this price.

It is in this environment that individual firm decisions regarding launch strategies are taken, aimed at ensuring revenue streams to generate a return on R&D investments, but cognisant of the interaction of global prices. Pricing and reimbursement regulations aimed at containing firms' monopoly rents, have the subsequent effect of delaying adoption of pharmaceutical innovation. It is important to recognise that these timing issues may have significant welfare impact, as delay to innovative medicines prevents access to potentially beneficial products, which can have detrimental population health effects.

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

2 BACKGROUND

Thus pharmaceutical products typically face a number of regulatory hurdles; evidence on the quality, safety and efficacy of new molecules is estimated to take around ten-years of pre-clinical and clinical research time (Permanand, 2006). Following review of the new product dossier by a regulatory authority such as the Food and Drug Authority (FDA) in the USA or the European Medicines Agency (EMA) in the EC, marketing authority is established, which defines the relevant patient population and therapeutic use.

Lags in the adoption of innovative pharmaceutical products are then the result of different influences in different countries, but of great importance are local price and reimbursement regulations. Several studies in the literature have addressed delays attributable to drug review processes generally (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 (see for example Danzon and Epstein, 2008; Lanjouw, 2005).

These latter studies defined price and reimbursement controls in two basic ways. The first way, as used by Lanjouw (2005) uses treatment dummies to identify the presence of price controls exist at the time of launch. Similalrly, Mejer et al. (2007) use dichotomous variable approach to identify both direct price regulations (international price comparisons, therapeutic value/cost-effectiveness, pharmaceutical contribution to the economy) and indirect price regulations (profit control, reference pricing). The latter is used in a discrete choice analysis to test how different pricing and reimbursement schemes affect the probability of launch for NCEs approved by the centralized EMA 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 a ranking of price bands and regulation dummies to indicate whether prescription budgets, reference pricing, price freezes and controls affect launch times. Studies using this first definition 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) further observes that launch in a price-controlled country significantly reduces the likelihood of introducing products in additional markets.

Treatment dummies and price ranking, control for regulation only approximately and are potentially inaccurate given the dynamic and multidimensional nature of regulation. Price ranking, for example, may be highly heterogeneous with respect to therapeutic subgroups or across time. In addition, treatment dummies frequently exhibit multicollinearity with country effects. Partly in reaction to these criticisms, there is a newer, preliminary body of literature which has incorporated product-specific data on actual prices to identify the impact of regulation empirically.

These newer studies differ broadly in how they define product prices, and tend to emphasise the formulation of firm's expectations over how price and reimbursement controls will affect price on entry. Danzon et al (2005) proxy expected price by the lagged average price per standard unit (SU)[1] for the therapeutic class (ATC3) in quarters 3 and 4 prior to the first global launch, in an attempt to capture a firm's expectation over the impact of price controls. While Danzon and Esptein (2008) use the average competitor prices in the therapeutic class (at the finer ATC4 level) prior to local launch as a measure of this expectation. In terms of specification Danzon et al. (2005) use the continuous time Cox proportional hazard (PH) model whereas the latter study uses discrete-time implementation of the PH model by complementary log-log regression. Findings from the second category of studies, which use explicit definitions of expected product price, suggest that the hazard of launch is positively related to expected price, once again implying that price controls have a negative impact on launch timings.

In addition to regulatory market barriers, late entry may reflect strategic firm behaviour to avoid the effects of price spillovers due to reference pricing and parallel trade. Danzon et al (2005) proxy such spillover effects through overall, market size,

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

identifying a significant market size effect. Whereas Danzon and Epstein (2008) conclude total volume of drugs in a therapeutic subgroup is not a significant factor affecting launch time.

We utilise the approach of these later studies to be more explicit in analysing pharmaceutical product launch times and price spillovers in a large set of newly marketed molecules, and across a wider set of global launches than previously considered.

3 METHODS

3.1 Data

Intercontinental Medical Statistics (IMS) data are used with quarterly sales data, in US$, over the period 1999 (Q1) – 2008 (Q3). The data used relates to standard unit (SU) sales of new molecules in 13 different ATC1 therapeutic categories during 1999 Q1 – 2008 Q3.[2] The dataset comprises 20 countries, which represent the major pharmaceutical markets in the OECD (plus South Africa)[3]. Each product is identified by the molecule name, IMS generic classification, global and local launch dates, therapeutic class (ATC4)[4], and breakdown of sales by the distribution channel (retail versus hospital). Spain, Turkey, Belgium, Greece, Portugal, Spain, South Africa have only retail channel data[5]; in Sweden retail and hospital sales are combined.

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. The unit of analysis is molecule-country pairs. The time to launch for each 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 dataset is expanded to define

[2] ATC1 therapeutic category is the Anatomical Therapeutic Category classification code for pharmaceuticals. Each ATC category stands for a pharmaceutical substance use in a single indication within 13 general categories of use. Finer classifications exist through five levels; ATC1 – ATC 5.
[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] We are happy to release the name of each group and product upon request.
[5] Launch in these countries therefore represents launch in the retail sector.

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. Our empirical strategy takes advantage of the variation in launch dates which is attributable to the various expectations held by producers over the price and sales volume attainable in individual markets, the regulatory rules, and the degree of market competition.

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, and our analysis is more complete in this respect. Our sample contains molecules that launched after 1999, and the total number of molecules in this set is 22,397, with the median time to launch being 14 months.

The analysis uses ex-manufacturer price levels, that is any marketing discounts and mark-ups across the wholesaler and retailer sectors are ignored and we focus on the regulated price. The price for all molecules is calculated by dividing the ex-manufacturer total revenue by volume in SU sales. In Spain, Turkey, Belgium, Greece, Portugal, and South Africa generic launch is always within the pharmacy distribution chain. In Sweden launch could be either in the pharmacy or in hospital. For all remaining markets, IMS data includes retail prescription, pharmacy and hospital data. Obviously, given the range of discounts and co-payments that apply across these different sectors our calculated price will only ever proxy the true selling prices, but the ex-manufacturing price is the price at which national price regulations are negotiated. Moreover, estimated country fixed effects should account for some of the variation in country specific discounts. Quarterly average price is assumed for each month in a given quarter, and the price calculated essentially estimates a volume weighted average price for each molecule across all products with the same active ingredient.

Further (confounding) variables are defined using the IMS data on sales, including an Herfindahl-Hirschman Index of global market competition, firm size as proxied by

sales volume, and product quality as established by molecule characteristics. OECD statistical extracts were obtained for additional data on GDP per capita[6]. Sales data was deflated using GDP deflators from the International Monetary Fund World Economic Outlook Database 2008[7],[8]. A list of descriptive statistics is provided in Table 1, with the appropriate log values were used in the model described below.

3.2 Model

Entry of a product into a given country, relative to the initial global entry, is treated as a binary outcome. By attaching dates to this binary-outcome (launch) event, we can define whether or not launch in a given market has occurred during any given time interval and condition this on a number of factors, including the expected product price as determined by the regulatory environment, the degree of product competition and product quality. We use the timing of entry to estimate the conditional probability of launch during interval *t*, (i.e. in standard survival terms, this is the interval hazard rate).

We use a complementary log-log (cloglog) function to estimate the time to launch. The cloglog transformation is a discrete-time implementation of the Cox proportional hazard (PH) model that assumes continuous time lapse to a pre-defined event, in our case launch date. It is typically used when time to an event is measured continuously, but grouped on a discrete time scale (e.g. months, as in this study) and when data are highly skewed (as is the case with launch times).

The formal model is specified as:

$$F(\mathbf{z}\boldsymbol{\beta}_{jkt} + \gamma_t) = 1 - \exp\left\{-\exp(\mathbf{z}\boldsymbol{\beta}_{jkt} + \gamma_t)\right\}$$

where $F(.)$ is the cumulative binomial distribution function of launch times, which is a function of explanatory variables *z*, each indexed by molecule (*j*), country (*k*) and monthly time-period (*t*), and γ_t is a duration dependence (time effect) parameter

[6] Available at http://stats.oecd.org/index.aspx
[7] 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.
[8] Real sales figures were calculated as: Real Sales = Nominal Sales*100/GDP deflator

measuring the extent that probability of launch occurring is increasing (or decreasing) over time. This specification is associated with the launch rate (i.e the hazard rate) within any given month (*t*) as:

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

The duration dependence parameter, γ_t, assumes a crucial role in determining the probability of launch. Our empirical strategy specifies two different duration specifications for this parameter: (i) a parametric specification where $\gamma_t = f(\gamma)$, with *t* corresponding to the number of months passed since potential launch date (i.e. first global molecule adoption); specifically we assume duration dependence is modelled by the number of months passed since potential launch date plus a quadratic term, $t + \ln(t^2)$, and (ii) a semi-parametric specification that includes dummies for each month following the possibility of potential launch. Essentially the semi-parametric specification provides a robustness check of any potential bias arising from duration dependence being incorrectly specified[9].

Within the matrix of explanatory variables, *z*, we explicitly consider molecule launch times are conditioned on expected prices as a reflection of regulatory impact, market competition, market size and molecule and firm characteristics. We now detail each of these aspects individually[10]. The net effect of regulation is defined by expected launch prices, given that we note above that 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.

[9] We allow duration dependence parameters to be flexible and not directly account for unobserved heterogeneity (see Backer and Melino, 2000).

[10] The impact of one unit change in price (p) on probability of launch (h) is computed as $\partial h/\partial p = (\partial h/\partial \ln(p)) \cdot (\partial \ln(p)/\partial p) = (\partial h/\partial \ln(p)) \cdot (1/p)$ which equals (the marginal effect) · (1/p). Similarly, the impact of one standard deviation in price on the hazard of launch is estimated as (std dev)·(Marginal Effect from Regression)·(1/p)

The expected market size for a new molecule, reflecting both the importance of the market and the potential spillover effects, is defined as quarterly lagged total SU sales within the molecule's ATC4 in individual markets. The ATC4 classification is used to define the potential market as competition and substitution effects are assumed strongest at this level[11].

Competition, proxied by a calculated Herfindahl-Hirschman Index (I_{HH}), is also assumed to exert influence on the likelihood of launch. . The index, 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.

The competition effect, as measured by the concentration index, is ambiguous. High concentration is held to reduce the equilibrium level of entry in most industries. No prior study has tested this in the pharmaceutical sector by specifically considering the impact of concentration on the hazard of launch at a molecule subgroup level of analysis. High concentration among patent protected products within a molecule sub-group might reflect a barrier to entry, and subsequent longer than expected launch dates for new products. However, note that patent protection is for the NCE, not the product per se and firms may compete in this patent protected market through emphasis on product quality and product characteristics. Moreover, as the production process for new prescription drugs occurs over a long development period with high sunk development costs and low distribution costs once a molecule is developed (DiMassi et al 2003), it is expected that companies would wish to launch as quickly as possible (Danzon and Epstein, 2008). Indeed the evidence on the effect of competition in the patent-protected markets suggests that competition incentivises entry (Kyle 2007).

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 with whom they have frequent dealings (Carpenter and Turenne, 2004). Similarly, scale effects suggest an advantage in promotional activities that may

[11] When molecule -country fixed effects where specified we did not find a significantly different effect in the price coefficient.

influence physician-prescribing levels. Economies of scope imply knowledge spillovers across different drugs and markets. Learning effects through multiple launches in a given market can enable firms to effect more efficient launch strategies. Larger firms may therefore have better prospects of entry in any given market. Therapeutic quality is the main factor that defines product differentiation and strategic positioning of a new pharmaceutical technology, yet one cannot assume that all products are cost-effective and hence conductive to better quality of care. However, the therapeutic importance of molecules is found to affect 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. The level of a molecule's global sales in 2007 is used as a proxy to control for molecule characteristics since therapeutic importance and commercial success are highly positively correlated.

4 RESULTS

Table 2 presents base case estimates of the marginal effects gained from the cloglog specification for molecules that first launched globally after 1993. The results are presented both with respect to the quadratic duration specification with a second-order polynomial in time since global launch, and a semi-parametric specification as described above. Tests for the proportional hazard assumption are supportive ($p>0.20$).

Our main result focus on the impact of price regulation on the timing of the launch of a new molecule is significant and strongly robust across these specifications. In all regression specifications the estimates for our measure of the impact of price regulation, the expected price, after controlling for 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 2). This is close in value to 0.0053, the marginal effect of expected price for superior molecules reported in Danzon and Epstein (2008). Standard error estimates of expected price are slightly lower because we cluster by molecule-country rather

than by molecule alone. The latter is expected given the presence of price (regulation) benchmarking across countries with are specific for each molecule.

With respect to other effects, for competition, 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. In other words, and in common with many other industries, the higher the concentration, the lower is the likelihood of rapid launch. Firm heterogeneity, proxied by the number of countries[12] a firm has launched in, 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) reduces the probability of delay by 0.011. This is close to the 0.009 estimate of Kyle (2007). With respect to molecule characteristics, a unit increase in the log molecule sales globally increases the hazard of launch by 0.004. 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. The only caveat of our approach is that it might introduce a bias for older molecules as they have had more observed time to launch to more market, although we do control for time since first global launch. The effect of country income, as given by log GDP per capita ($) is positive but not significant, and is therefore excluded from some specifications.

Finally, time may affect regression estimates in several ways. First, macroeconomic trends in the sector may have an impact on price levels, so we account for this 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 therefore captured by interacting expected

[12] The number of countries a product has launched is a proxy of quality in the sense that the treatment has managed to go through the recommendations of professional societies of different countries. However, it could well be due to differences in gaps in knowledge, yet other controls do measure such effects.

price, as well as volume with the time since global launch. A dummy variable (First Launch Before 1999) is also 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 1993 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 precise model specification (see Table 2).

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).

Given that we use proxies for a number of our confounding variables, we carry out a number of robustness checks. With respect to competition effects we carry out robustness checks by controlling for the number of substitute molecules and investigate whether generic competition is significant (fully reported as Appendix Table 1). 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, as compared to the extent of generic competition proxied by the number of substitute molecules with generic competition. This is 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.

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 (fully reported in Appendix Table 2). 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.

In the robustness checks, on molecule characteristics we further proxied therapeutic importance using the total number of markets in which a molecule has launched, i.e. global extent of launch (fully reported in Appendix Table 3).
Finally, we also wish to explicitly test for the potential impact of price interdependency across country markets. We therefore restricted the country set to EU countries to assess this impact and report the results in Table 3. We find strong evidence that external reference pricing slows adoption of innovation. Launch in a high-priced EU market increases the conditional probability of launch 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 4). 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.

Thus to summarise, regardless of the precise time duration specification, and controlling for a large number of confounding effects, price regulatory controls on reimbursement have a strong effect on time to launch. Across a range of specifications and definitions, we also find weak 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. We further find that within the confines of the EC market where, although individual countries have their own price and reimbursement authorities there is considerable cross-referencing of pharmaceutical prices and parallel importing of pharmaceutical products, price regulatory spillover effects appear to have an impact on launch times.

5. DISCUSSION AND CONLCUDING REMARKS

This paper makes several contributions to the literature on the effects of regulation on the launch of new medicines. First, through exploiting the variation both over time and molecule-country pairs in a larger set of launch countries and taking advantage of a richer set of variables than previous research. We also perform subsample analysis on a sample of European Union countries to capture the potential effect of price spillovers when price benchmarking is in place. We have estimated different duration specifications and used alternative proxies for risk factors to assess the robustness of the results. The dataset is thus the most comprehensive and up-to-date than comparable empirical studies in the literature, and contains more extensive controls, both in terms of control variables and the time period analysed. The analysis also makes use of firm and molecule heterogeneity that could bias estimates of the impact of price regulation if omitted. Finally, the analysis is carried out for potentially global molecules in this set of countries ensuring findings are relevant for a sample of innovative products and not restricted to an average sample of drugs that might include products of lesser therapeutic value, thus biasing the analysis of product launch times.

Our results suggest a statistically significant and robust effect of price and reimbursement regulation on launch delay, as analysed through the expected price firms believe they will achieve in different jurisdictions. Furthermore, given that external reference pricing regulations create price linkages across markets, we

conclude that regulation might also indirectly result in delayed access to pharmaceutical innovation through that mechanism. Consistent with earlier evidence, we also find that greater concentration leads to longer launch times, which confirms the importance of policies directed at fostering competition in the pharmaceutical sector. We finally observe a significant and robust market size effect that decreases the launch time of new pharmaceutical products as market size increases.

Nonetheless, we observe significant firm and molecule heterogeneity in the speed of launch. In particular, firm economies of scale and a molecule's therapeutic importance grant substantial advantages for launch times internationally. Contrary to findings in the literature, we find no significant advantage to domestic launch. Findings in this paper suggest several policy implications. First, price regulations appear to result in a decrease in timely pharmaceutical adoption on a global scale, especially if there are price interdependencies. This may impose welfare losses, particularly when the innovations that are delayed are cost-effective therapies from a societal perspective. 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).

Delays in adoption also reduce the net present value of R&D investments by delaying cash flows and shortening the exclusivity period, which could reduce future R&D and innovation (Giaccotto et al., 2005). Although price controls may therefore increase static efficiency in the short term by driving prices and marginal costs closer, they could also result in potential longer-term losses in dynamic efficiency due to the reduced incentives associated with market entry. This study therefore highlights the importance of ensuring price and reimbursement regulation is efficient in this sector, not least as the regulation itself can have important spillover effects across countries. Our analysis also confirms greater concentration leads to longer launch times. To the extent that extensive price controls may reduce incentives to entry, they may play a further role in delaying pharmaceutical product market launch. Finally, due to scale

advantages in international rollout strategies, price controls may have helped increase the incentives for mergers and acquisitions, further increasing concentration levels and barriers to entry (LaMattina, 2011).

From a policy perspective, the results are suggestive that price regulation does exert an influence on the company's timing decision in entering a market. However, our results rely on official data that do not contain potential rebates. Such rebates might be an important strategic tool used by manufacturer companies to manage and promote the diffusion of its product, while at the same time keeping the official price high. Such a strategy is of importance when price regulation spillovers exist through price benchmarking. While a limitation of this study, it is a general data limitation given the lack of source material on discounts in this sector.

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TABLES

Table 1 Variable Definitions and Descriptive Statistics for the Data used in Survival Analysis

External Environment	**Variable Name**		
Regulatory Environment		*Mean*	*Std Dev*
Expected Price	Average Price per SU of non-generic products in the therapeutic class (defined at country-ATC4 level)[a]	$42.9	$174.9
Relative Price	Relative Price to the highest in the EU[b]	0.29	0.46
Price Setting	External Referencing (Binary variable indicating whether external reference pricing is applied; defined at country level)	0.83	0.37
Expected Market Size	Total Sales in SU (lagged 1-year) in the therapeutic class (defined at country-ATC4 level)	24,736,000	96,220,000
GDP per capita	GDP per capita ($)	$26,804	$8,080
Market Concentration	Log Molecule Concentration $I_{HH} = \sum_{i=1}^{N} \left(s_i^{\,2} \right)$, where s_i is the market share of molecule i and N is the number of molecules in the therapeutic subgroup (defined at country-ATC4 level)	10.058	1.158
Intermolecular Competition	Number of Molecules in the therapeutic class (defined at country-ATC4 level)	9.89	15.94
Generic Competition	No. of Molecules with Generic Competition in the therapeutic class (defined at country-ATC4 level)	7.85	16.25
Economies of Scope	Global Firm Sales ($) in 2007	$14.1million	$12.9million
	Number of Countries Firm has Launched in	16	7
Economies of	Firm's Total Number of Molecules	453.5	401

Scale			
	Local Firm Experience (number of molecules launched)	112	121.5
Location of Firm Headquarters	Domestic Launch	0.11	0.31
Therapeutic/Commercial Importance	Global Molecule Sales ($) in 2007	$357,758	$766,566
	Molecule's Global Reach (total markets launched in)	15	3
Period of Global Launch (old vs new)	First Global Launch Before 1999	0.67	0.47

Note: [a] All lags are by one quarter.[b] We defined this variable as a binary variable as based on Kyle (2007) (1 if high priced; 0 otherwise).

Table 2 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]
S.Africa	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]
USA	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

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

Standard errors (in brackets) clustered at country level

[a] Dummies available upon request

[b] For semi-parametric duration specification

T**able 3 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

Note: *p<0.05, **p < 0.01, ***p<0.001. Non-exponentiated parameter estimates reported . Country, ATC1 and calendar-year dummies included

Table 4 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)		-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

Note: *p<0.05, **p < 0.01, ***p<0.001. Non-exponentiated parameter estimates reported .

APPENDIX

Table A.1 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]	0.000001 [0.0011]	0.000001 [0.0010]
Log Number of Molecules with Generic Comp in Ctry-ATC4		0.000001 [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

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

Non-exponentiated parameter estimates reported

Table A.2 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

Note: *p<0.05, **p < 0.01, ***p<0.001. Non-exponentiated parameter estimates reported

Table A.3 Robustness Check: Molecule Characteristics

	Marginal Effects in Cloglog (quadratic in t)		
	1	2	4
Log Lagged Price/SU	0.0031*** [0.0006]	0.003*** [0.0006]	0.0031*** [0.0006]
Log Lagged Total SU in Ctry-ATC4	0.0022*** [0.0004]	0.0020*** [0.0004]	0.0020*** [0.0004]
Log Global Molecule Sales	0.0033*** [0.0005]		
Log Molecule's Global Reach		0.0592*** [0.0059]	0.0591*** [0.0058]
Log Lagged Avg Price/SU * ln(t)			-0.0012** [0.0003]
Log Lagged Total SU * ln(t)			-0.0013*** [0.0002]
First Launch Before 1999			-0.0103*** [0.0028]
Years since global launch (t)	0.0042*** [0.0011]	0.0041*** [0.0011]	0.011*** [0.0017]
Years since global launch squared	-0.0012*** [0.0001]	-0.0012*** [0.0001]	-0.001*** [0.0001]
Number of Obs	58279	58530	58530
LogLikelihood	-10433	-10485	-10467

Note: *p<0.05, **p < 0.01, ***p<0.001. Non-exponentiated parameter estimates reported.

Country, ATC1 and calendar-year dummies included