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Price regulation and relative delays in generic drug adoption

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ABSTRACT

Increasing the adoption of generic drugs has the potential to improve static efficiency in a health system without harming pharmaceutical innovation. However, very little is known about the timing of generic adoption and diffusion. No prior study has empirically examined the differential launch times of generics across a comprehensive set of markets, or more specifically the delays in country specific adoption of generics relative to the first country of (generic) adoption. Drawing on data containing significant country and product variation across a lengthy time period (1999–2008), we use duration analysis to examine relative delays, across countries, in the adoption of generic drugs. Our results suggest that price regulation has a significant effect on reducing the time to launch of generics, with faster adoption in higher priced markets. The latter result is dependent on the degree of competition and the expected market size.

1. Introduction

Generic drugs are cheaper alternatives to branded medicines offering the most visible source of efficiency gain to any health system.[1] Understanding the determinants of generic drug launch is important, given such potential cost savings. Yet there is surprisingly scarce empirical evidence on the timing of first generic entry following patent expiry, or the reasons explaining launch delays across major pharmaceutical markets. Given the limited potential for product differentiation, generic producers predominantly engage in price competition, which can result in lower market share for branded products. Generic prices are markedly lower than branded products as innovation costs are negligible. The cost of bioavailability tests, to establish generic status, are significantly cheaper than the average R&D costs required for branded products to establish safety and clinical efficacy. It is estimated that this alone allows generic prices to be some 20–80% cheaper than originators (Simoens and de Coster, 2006). Griliches and Cockburn (1994) observed that branded market share falls by approximately 50% within two years of patent expiry due to the impact of generic competition. Berndt and Aitken (2010) state that the generics share in retail prescriptions in the USA had risen from under 20% in the mid-1980s to approximately 75% by 2009. In Europe, evidence suggests that the average prices of pharmaceutical products in Europe fall by approximately 20% during the first year of loss of (patent) exclusivity, and a further 5% over the next two years again as a result of generic competition (DG Competition, 2009). As branded prices tend to remain high initially after generic entry, the latter effect is attributable to lower generic prices. These lower prices can result in a high market share being obtained by generics. In the UK and Germany generic market share (in prescription units) is around 60% in aggregate, although this falls to under 40% in a number of other European countries; e.g. Austria, Belgium, Ireland, Portugal, and Spain (European Generics Association, 2009).

Of course, not all consumers perceive generic products as having the same quality as incumbent branded products. Brand loyal, price-insensitive consumers and physicians may be reluctant to switch from brand-name drug use (Frank and Salkever, 1992; Hellerstein, 1998; Coscelli, 2000). To counteract such behaviour, regulations are commonly put in place to promote generic substitution and market entry. For example, to avoid delays to generic entry once patent protection expires, Bolar exemptions or safe harbour provisions, were introduced in the US (with the Hatch Waxman Act in 1984) and the EU (with EC Directive 2004/28),

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[1] A generic drug is a chemically bioequivalent to any originator reference product with similar qualitative and quantitative composition in active ingredients, same form, route of administration, safety, and efficacy profiles (Scott Morton, 1999; Lichtenberg and Philipson, 2002).

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allowing generic manufacturers to conduct research and bioequivalence studies prior to protected branded product patent expiry in preparation for regulatory approval.[2]

Overall, the time it takes a generic drug from research lab to market can be as short as 3–5 years. Yet generic entry often takes longer than might be expected on the basis of patent expiry and the statutory loss of exclusivity of the originator product (DG Competition, 2009). If countries impose price and reimbursement regulation on such products, generic drugs can incur substantial delays to market entry, limiting patient access and delaying potential cost-savings to health insurers and, ultimately consumers. In the EU for example, despite attempts to support competitive practices through increasing market harmonisation, time delays for licensed generics were found to be an average of 6 months following patent expiry (Bongers and Carradinha, 2009; Hudson, 2000). If generic entry had taken place immediately upon loss of exclusivity over the period 2000–2007, savings arising from price competition within the EC would have been approximately €3 billion according to a DG Competition report, as based on an assumed slightly longer average delay of 7 months (DG Competition, 2009).

We argue in this paper, that the variation in the timing of first generic availability across countries can be explained by producers' ex ante price and sales volume expectations, which are themselves influenced by country-specific regulations and levels of competition. We analyse the (country) specific delay in the adoption of generic drugs by defining individual country launch relative to the first international (generic) launch for 20 major pharmaceutical markets over the period 1999–2008. This period which saw the introduction of substantial new regulatory changes in a number of the major Organisation of Economic Cooperation and Development (OECD) pharmaceuticals markets, including the harmonisation of EC pharmaceutical regulations in 2001 (EC Directive 2001/83/EC). Our empirical strategy uses duration analysis to estimate the impact of regulation on the probability of launch by incorporating local expected generic price information (proxying *de facto* regulation), controlling for market size, expected competition, type of molecule (active ingredient), and firm heterogeneity. This is the first study to provide an empirical analysis of launch-times for generics across a comprehensive set of major pharmaceutical markets.

The paper is structured as follows: Section 2 discusses the literature and sets the framework; Section 3 describes the data and the methodology used; Section 4 presents estimation results and finally Section 5 discusses findings and policy implications.

2. Previous literature and background

The literature has revealed a complex array of factors affecting generic market entry and adoption. Early empirical studies from the USA highlighted, amongst other factors, the importance of pre-entry market size and expected profits (Grabowski and Vernon, 1992; Scott Morton, 1999, 2000; Reiffen and Ward, 2005), firm and drug characteristics (Bae, 1997; Scott Morton, 1999), the loyalty attached to brand-name (Hurwitz and Caves, 1988; Hudson, 2000), and market structure and competition (Bae, 1997). However, the importance of each of these factors in determining entry dynamics differs strongly across therapeutic-classes (Saha et al., 2006).

Of the early studies, Bae (1997) explicitly investigated the speed of generic entry after patent expiry in the US market using a time duration model, finding that high market revenues experienced by branded drugs prior to patent expiry were associated with a higher probability of generic entry. The same study finds that a higher degree of competition in a therapeutic market, as proxied by the number of incumbent brand-name competitors, is correlated with slower generic penetration. Scott Morton (2000) finds that while increased numbers of brand-named competitors reduce generic penetration, increased numbers of generic products do not. Conversely, Saha et al. (2006) finds that generic market strategic deterrence is associated with the relative number of generic incumbents. A more recent study observes that the number of brand name competitors is associated with a positive impact on generic entry in a sample of several countries including the US, UK, Germany, and France (Magazzini et al., 2004).

There is also evidence that the probability of generic entry and the associated generated revenue are positively related (Frank and Salkever, 1997). Hudson (2000) identifies market size (proxied by original brand sales) at patent expiration to be the most significant determinant of generic entry in the US, the UK, Germany, and Japan. For Japan specifically, Iizuka (2009) finds that, consistent with the findings of Saha et al. (2006), higher numbers of competitors in the market discourage generic entry, although economies of scope in entering multiple markets and brand revenues are important determinants of generic entry. The evidence, whilst patchy, is then that expected competition has an impact, although the importance of this impact has not been fully established, while the related aspects of expected revenue and market size also appear important to generic launch strategy.

Several studies have also highlighted the role played by pharmaceutical price regulation on the development of the market for branded pharmaceutical products (e.g. Danzon and Chao, 2000b; Ekelund and Persson, 2003). The evidence on the impact of *different* regulatory practices on generic entry has, however, received limited empirical attention. Evidence from the Swedish market suggests that higher anticipated profits are associated with higher generic entry in this (price) regulated market (Rudholm, 2001). Recently a number of European markets have introduced reference pricing regulation for generic products, where the reference price is generally computed from the lowest priced generic product(s), which has expanded the adoption of generic products (see Kanavos et al., 2008). Yet, there is some evidence of generic entry deterrence in reference priced countries (Ekelund and Persson, 2003; Kanavos et al., 2008; Simoens and de Coster, 2006). Others have found that price regulation generally appears to be associated with reduced incentives for generic entry, and limited diffusion after entry (Danzon and Chao, 2000a; Garattini and Ghislandi, 2006; Simoens and de Coster, 2006).

Generic producers tend to pursue price competition strategies. Regulation of the generic market can augment this price competition by introducing various instruments (e.g. reference prices, lower cost sharing or higher pharmacist mark-ups for generic products) that attempt to lower prices for both branded and generic products after patent expiry. Given the potential loss in market share arising from generic entry, not surprisingly, innovator companies have developed several strategies to minimise this impact on the life-cycle profits of branded products, as documented by a number of studies (Appelt, 2009; Aronsson et al., 2001; Caves et al., 1991; Frank and Salkever, 1997; Grabowski and Vernon, 1992; Hollis, 2003; FTC, 2002a,b; Lexchin, 2006; Karwal, 2006; Magazzini et al., 2004; Suh et al., 1998; Wrowleski, 2002). Strategies include the combination of multiple patents into patent clusters, pursuit of litigation over the reformulation of the original molecule and expansion of patent protection. In some countries where direct to

[2] The adoption of similar regulations as the Bolar exemptions by Germany and the UK for example, has also meant that generic medicines can obtain immediate price and reimbursement approval from health insurance authorities following market authorisation in those countries. The passage of the Patent Protection and Affordable Care Act (2010) in the USA is likely to further ease market entry for generics in this major market (Berndt and Aitken, 2010).

consumer advertising is banned for prescription drugs, marketing strategies include switching from prescription to over-the-counter (OTC) targeting. In freely priced markets, the originator may simply increase off-patent molecule prices to capture more revenue from the insensitive segment of the market (Frank and Salkever, 1992, 1997; Regan, 2007; Scherer, 1993; Schweitzer and Comanor, 2007). There also exist cooperative strategies, such as the development of alliances between brand-name producers and generic companies (Scottorn, 2009), and the so-called 'pay-for-delay' tactic where branded companies pay potential generic competitors to stay out of the market (FTC, 2010). All such responses highlight the impact that generic pricing entry can have, and the role that competitor strategies may play in affecting market entry, even where there are regulated environments in place.

However, the design of appropriate market incentives is far from straightforward and the understanding of the impact of generic products in specific pharmaceutical markets is low. Berndt and Aitken (2010) document the complexities with respect to the US market, the most important generic market globally. While Danzon and Furukawa (2011), considering 10 high- and middle-income countries, find that generic products in countries where physicians retain prescribing rights exhibit higher prices and lower volume of up-take, compared to countries where pharmacies have dispensing rights (which tend to be correlated with generic substitution).

Our paper adds to this literature, using a large data set across a substantial time-period to explore empirically generic drug launch times in the major pharmaceutical markets. Given the importance of price setting and price regulation, we are specifically interested in the impact that expected generic prices have on the timing of launch decisions, controlling for market, product and firm characteristics.

3. Data and methods

3.1. Data

Intercontinental Medical Statistics (IMS) data are used with quarterly sales data over the period 1999 (Q1)–2008 (Q3) in 20 major pharmaceutical markets (US, Canada, Germany, Italy, France, Spain, UK, Greece, Finland, Austria, Turkey, Sweden, Japan, the Netherlands, Poland, Italy, Belgium, Switzerland, Finland, Portugal) which regularly experience early launch of generics after patent expiry.[3] The data include estimates of sales in USD ($) and standard units (SU) for nearly 350 pharmaceutical products by quarter, their molecule name, generic classification, global and local launch dates, therapeutic class (ATC4),[4] and sales by distribution channel (mainly pharmacy prescription versus hospital networks). 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 of generics, but the ex-manufacturing price is the price at which national price regulations are negotiated.

The unit of analysis is molecule-country pairs. Once the generic version of a given molecule launches in one of the twenty markets, the remaining countries are classified as potential future markets for further launch of the generic version of the same molecule. This definition allows analysis of differentials in relative adoption speed with reference to the first global generic availability.

Given the domination of multinationals in the pharmaceutical sector, the development of Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 2001 and the increasing adoption of international clinical trials for individual compounds used to file for market approval in many countries simultaneously, we expect actual patent protection for the same branded product in the vast majority of cases to have relatively minor variation across different markets. All countries in our sample are subject to 20-year patent agreements, but these may be eroded in a variety of ways due to, for example, the varying lengths of clinical trials (and note that key patents may be applied for early in the trial period giving added importance to trial length), and to some extent by reimbursement regulation. These erosions may, in turn, be compensated by patent extensions of up to 5 years in the USA and Europe. These extensions are themselves subject to maximum patent periods, with the patent period from market authorisation not exceeding 14 or 15 years in the USA and Europe respectively. Although data restrictions mean that we cannot directly estimate the delay following actual patent expiry, we can measure the delay of the originator entry following the first global launch of the new molecule, which we presume to be a reasonable proxy of the actual patent expiry date.

We define the delay in generic launch for molecule *j*-country *k* pair as the difference between the first global generic launch date of molecule *j* and the local launch date of the generic in the country *k*. Thus our empirical strategy takes advantage of the variation in generic launch dates which is attributable, not to a variation in patent expiry across markets, but to the various expectations held by generic producers over the price and sales volume attainable in individual markets, the regulatory rules, and the degree of market competition. Strictly speaking, this is from the time of first launch of a generic in any major global market, but as noted, this will be highly correlated with patent expiry. Given the communality of patent protection that exists in the major markets studied, this is not an exacting assumption.

We restrict the molecule set in this study to those molecules that have a generic alternative in the two main markets (US and UK), to build a standardised sample of products and avoid potential biases from generics launched exclusively in a single market. Our sample contains molecules that launched following the establishment of a Single European Act in 1992, leading to a common European market in 1993. Combination molecules composed of several active ingredients are also ignored. With these restrictions, the total number of molecules examined is 349, all of which are analysed for several countries, and where launch delays are computed empirically as described above. This data set is expanded through the creation of a number of price, regulatory, market structure, competition and product and firm characteristics as described below.

3.2. Model

We model entry of a generic product in a given country, relative to the initial global entry, treating this 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. We use the timing of entry to estimate the

[3] Although some countries such as Spain or Italy did not adhere to patent regulation until 1992, the period and countries selected allows for the identification of generic products as opposed to copies (Costa-Font and Puig-Junoy, 2004).

[4] The Anatomical Therapeutic Chemical (ATC) classification system divides drugs into different groups according human body system on which they act and their chemical, pharmacological and therapeutic properties. ATC4 denotes the same chemical subgroup.

conditional probability of launch during interval t (i.e. in standard survival terms, this is the interval hazard rate).

We estimate the time to launch using a complementary log–log (cloglog) function. The cloglog transformation is a discrete-time implementation of the Cox proportional hazard (PH) model that assumes continuous time 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 in this study) and when data are highly skewed (as is the case with launch times).

The formal model is specified as follows:

$$F(z_{jkt}\beta + \gamma_t) = 1 - \exp\left\{-\exp(z_{jkt}\beta + \gamma_t)\right\}$$

where $F(.)$ is the cumulative 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 that measures the extent to which the probability of the launch event occurring is increasing (or decreasing) over time.[5] This specification is associated with the launch rate within any given month (t) given as:

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

or

$$\text{cloglog}(h_{jkt}) = \mathbf{z}_{jkt}\beta + \gamma_t$$

The duration dependence parameter (γ_t), plays a crucial role in determining the probability of launch. Our empirical strategy assumes 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 generic 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.

Within the matrix of explanatory variables z, we explicitly consider generic drug 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.[6]

3.3. Regulation and expected generic prices

Regulatory complexity and diversity are assumed to influence generic penetration and the price adopted. In the vast majority of European countries, generic prices are subject to some form of direct regulation. Upon entry, generic prices tend to be set through a reference price mechanism, either as a percentage of the originator price level, or as the average (generic) price in a selection of European countries which they have already been launched, or sometimes as a combination of both. In markets with reference pricing, regulators set a common reimbursement level for a group of interchangeable medicines, which once fixed, may constitute a barrier to further price competition (Dylst and Simoens, 2010). Even in markets such as the US, where generic prices are determined freely, they are related to branded prices, for example through setting the generic price as a percentage (normally 30–35%) of branded products, and will be affected by the regulation of distribution and cost-sharing agreements imposed by insurers.

Given the extensive price regulation of the pharmaceutical sector, price information has commonly been used to explain patent-protected molecule entry into various markets (cf. Danzon and Epstein, 2008; Kyle, 2007). Such an approach is arguably even more justified for generic products, given that generic prices may be regulated directly as well as indirectly, as incumbent brand prices are used to benchmark generic prices. Studies have found an indirect impact of price regulation, with the market share captured by generics depending on the relative prices of the generic to the originator (patented) product. Anis et al. (2003), for example, uses the generic-branded price ratio (Pg/Pb), as a measure of how price regulation affects generic penetration. This ratio (Pg/Pb) is observed to decrease significantly over time as new generics enter the market (Caves et al., 1991; Grabowski and Vernon, 1992). As with branded products, we therefore expect that more lax regulation (controlling for market conditions, firm size and product characteristics) will correlate with reduced launch delays.

We follow the general approach adopted by Anis et al. (2003) and estimate the influence of price on launch delay by defining the expected generic price as the average branded price of a molecule weighted by the median generic-branded price ratio in the local market for each molecule.[7] Five year moving average prices for all components of the definition are used to avoid problems of endogeneity. Finally, this expected price is used in logarithmic form in our estimations. Put simply, we assume that the generic manufacturers' expected price is a function of the existing branded product price weighted by the "average" generic-branded mark-up in the local market for all products which act as generic substitutes. For robustness checks we also computed the generic to branded price ratio and a 5-year moving average retail price of the branded product (in logs) as alternative measures of the price expectation of the generic manufacturers.

All such measures of price expectation are assumed to incorporate realisations of country specific regulations. In this way we can reflect the complexities and changes in country specific regulations over time. Focus on a single measure and expected price is common practice in the literature, to incorporate the myriad of regulations over time and across countries, which have affected generic, launch times. We also, however, incorporate country specific and time fixed effects in our specifications, which will capture elements of change in these regulations. We further test the robustness of the approach by examining correlations of our expected price variable with specific indicator variables for the presence and absence of particular regulations in individual countries, for example reference price regulations.

3.4. Expected market size, market structure and competition

Generics have lower net profit margins compared to non-generic products and maybe subject to intense price competition. The sustainability of the generic business therefore depends on capturing a high market share. Expected generic sales are a function of branded molecule sales prior to launch and expected generic

[5] The duration dependence parameter will also capture any unobserved heterogeneity in the data.

[6] The impact of one unit change in price (p) on probability of launch (h) is computed as $dh/dp = (dh/d\ln(p)) \times (d\ln(p)/dp) = (dh/d\ln(p)) \times (1/p)$ 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).

[7] The average branded product price in each country is calculated as a volume-weighted price of branded products that have the same molecule.

penetration following market entry. Previous studies (e.g. Costa-Font et al., 2014; Frank and Salkever, 1997; Iizuka, 2009) have ignored the differentials in generic market penetration and have predominantly used branded sales as a proxy for expected sales. We estimate expected generic market size as the product of total molecule units sold prior to generic entry and the average market share captured by generics. Average generic market share for each country is calculated over all molecules with generic competition in individual markets. Market size is estimated in purchasing power parity adjusted USD ($), although an alternative measure based on IMS standard units (SUs) is employed in robustness tests. Given that the marginal cost of producing and switching to generic drugs is relatively low, ex ante expectations for market competition were captured through a Herfindahl-Hirschman concentration index (HHI), which was calculated using the number of different products operating in the same therapeutic category within any given country.[8]

3.5. Firm and molecule characteristics

We control for heterogeneity in firm size by the quarterly, local and global firm sales volume, and global reach of the firm as proxied by the number of markets in which the firm has recorded sales (across the 20 countries in the dataset).

It seems reasonable to expect, ceteris paribus, molecules with high therapeutic value to diffuse quicker internationally. These molecules are important insofar as they offer a greater market potential for generic entrants. The total number of markets in which the molecule has launched is used as a proxy for relative therapeutic importance (although this depends on regulation and company characteristics). In addition, post-launch median sales over 1999–2008 and annual sales of the molecule (USD$) are used as additional proxies, with the latter used as robustness checks.

The evidence regarding product loyalty on generic entry is mixed. Rudholm (2001) finds that a longer monopoly period reduces entry, whereas Grabowski and Vernon (1992) found no significant effect of patent protection duration. Given the limited information available on molecule protection expiry dates, we cannot directly control for the exclusivity period in each market. However, launch delays (time lapse between the first global launch date and local launch date of the branded product) are used as a proxy, encompass delays in generic launch. The descriptive statistics for the main (untransformed) variables used in the analysis are provided in Table 1.[9]

Table 1
Variable definition and descriptive statistics (249 products, distributed over 20 countries throughout 1999–2008).

Description	Mean	Std. dev.
Non-generic retail price (molecule)	$9.58	$45.04
Expected price ratio [price of the generic product/price of the originator]	$0.770	$3.75
Expected generic price [log branded product price × (median of the generic price to branded price ratio)]	$0.293	$0.225
Average molecule sales in individual country ($1000)	$43,308	$148,805
Average generic share (by $ share)	38.5%	12.1%
Average number of (country) markets molecule has launched in	16	4
Average number of years between global launch and launch in next country	1.3	1.3
Average number of countries in which a firm operates	12	8

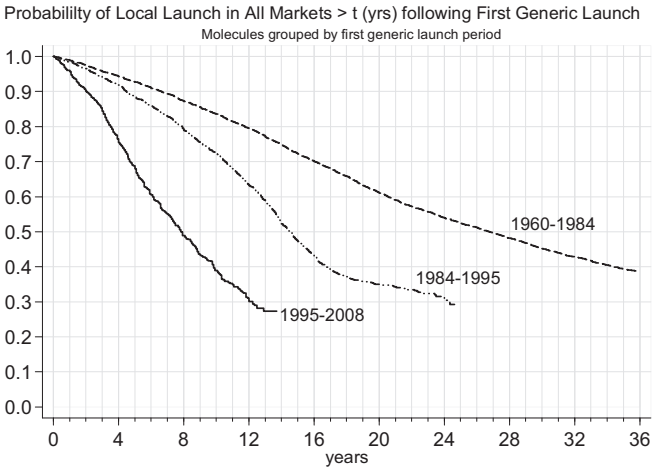

Fig. 1. Time to launch of generic molecules. *Note*: The graph shows overall median delays for generic molecules that launched globally in the US or UK from 1960 to 2008. The 3 lines represent molecule subgroups that have their first generic launch following global launch in the USA or UK in each corresponding period. The *y*-axis [$S(t)$], represents the probability that the event of interest [local launch of the generic molecule] has not occurred by time t on the *x*-axis.

4. Results

4.1. Preliminary evidence

We begin by examining, the distribution of time since first launch for generic drugs. Fig. 1 displays for three different time periods the probability of launch time for generic products in any market following (first) global launch. It does so for three distinct periods; the first (1960–1984) prior to the introduction of the Hatch Waxman Act (1984) in the USA; the second graphs the subsequent 10-year period (1985–1994); and finally the third graph refers to the period (1995–2008) covering our data. As can be seen by these crude estimates, generic launch times have fallen dramatically over time giving a *prima facia* case for investigation. Focussing on the recent period (1995–2008) Fig. 2 displays the distribution of generic launch times by country 1995–2008.[10] A clear pattern can be observed over the period, namely it appears that those countries commonly characterised as having less pricing regulation (that is Germany, the UK and the USA), appear to have faster launch times than those other countries displayed (which are characterised as having stricter regulation).

To investigate further the role of regulation on the up-take of generic medicines, as outlined above, the empirical strategy adopts a cloglog model with different econometric specifications.[11] In our main results duration dependence is specified parametrically as a function of time t, lapsed since launch. It has been shown that if the conditional probability of an event occurring is small, as turns out to

[8] An alternative measure of competition was based simply on the number of generic manufacturers in each country market, but introduced multicollinearity and was not pursued.

[9] A list of all calculated variables used for the regressions is available on request from the authors.

[10] The data used for our econometric analysis, with pricing product and firm characteristics are only available from 1999 up to 2008 and represents a sub-set of this data.

[11] As noted in the Model section we use 2 specifications of duration dependence, a large number of competing variables to proxy the various direct and indirect effects of regulation and confounding effects. These serve to test the robustness of our results. For the sake of brevity we focus on a sub-set of these results in the paper and make available a wider set of results in an on-line Appendix.

Table 2
Marginal effects of regulatory impact derived from expected price models: (cloglog with parametric time duration specification).

	(2.1)	(2.2)	(2.3)	(2.4)	(2.5)	(2.6)
Moving av. (expected) generic price (log of 5-year moving av. of branded price × median generic-branded price ratio)	0.002*** [0.0006]	0.003** [0.0010]		0.003*** [0.0006]	0.005*** [0.0012]	
Moving av. brand price (log of 5-year moving av. brand price)			0.002** [0.0006]*			0.002*** [0.0006]
Expected price ratio (price generic/price originator)			0.00001 [0.0133]			−0.022 [0.0147]
Expected market size (US $ sales)	0.002* [0.0007]			0.004*** [0.0009]		
Expected market size (standard units)		0.001 [0.0007]			0.003*** [0.0009]	
Moving av. of molecule sales in country (US $)			0.002* [0.0007]			0.003*** [0.0008]
Average generic share of market (US $)			0.000 [0.0002]			0.001*** [0.0002]
HHI (normalised)	0.009*** [0.0008]	0.009*** [0.0008]	0.009*** [0.0008]	0.011*** [0.0009]	0.011*** [0.0009]	0.010*** [0.0008]
Molecule annual global sales (US $) (log)	−0.001	0.0001	−0.001 [0.0009]	−0.002* [0.0010]	−0.001 [0.0010]	−0.002 [0.0010]
Years lag (log)	0.001 [0.0010]	0.001 [0.0010]	0.001 [0.0010]	−0.001 [0.0011]	−0.001 [0.0011]	−0.001 [0.0010]
Global firm sales (log)	0.0002 [0.0003]	0.00022 [0.0003]	0.0002 [0.0003]	0.0002 [0.0004]	0.0002 [0.0004]	0.0002 [0.0003]
Duration dependence in years	0.000*** [0.0001]	0.0001*** [0.0001]	0.0001** [0.0001]	0.001*** [0.0001]	0.001*** [0.0001]	0.001*** [0.0001]
Duration dependence in years^2 (log)	−0.005*** [0.0006]	−0.005*** [0.0006]	−0.005*** [0.0005]	−0.007*** [0.0006]	−0.007*** [0.0006]	−0.007*** [0.0006]
ATC1 dummies	Yes	Yes	Yes	Yes	Yes	Yes
Country dummies	Yes	Yes	Yes	Yes	Yes	Yes
Calendar year dummies	Yes	Yes	Yes	No	No	No
Number of observations	19,698	19,698	19,698	19,698	19,698	19,698
Log likelihood	−2083.37	−2086.36	−2083.47	−2192.41	−2199.68	−2170.06
X^2	798.35	798.11	817.25	617.43	604.45	615.58
Akaike info criteria	4260.73	4266.72	4264.94	4462.82	4477.37	4422.13
Bayesian info criteria	4631.48	4637.47	4651.46	4770.46	4785.01	4745.55

Note: Standard errors clustered at molecule-country level (standard errors in brackets). Marginal effects (dy/dx) reported. Year, ATC1 and country dummies not reported.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

be in our case, the cloglog specification yields similar estimates to a logit model of discrete time events (Abbott, 1985). We therefore also analyse the data using a logit specification. We estimate the timing of generic adoption in each market following the first global launch of a generic version of the same formulation.

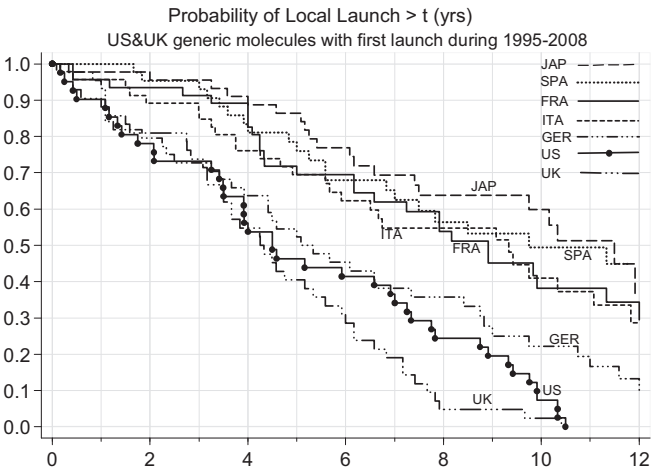

Fig. 2. Time to local launch following first generic launch. *Note*: The y-axis [$S(t)$], represents the probability that the event of interest [local launch of the generic molecule] has not occurred by time t on the x-axis.

Table 2 presents the marginal effects (dy/dx) for the parametric duration dependence specification given as $h_0(t) = t + \ln(t^2)$. The variable t indicates the number of months elapsed since the first global generic launch of the originator molecule. The log (t^2) coefficients support the view that the probability of launch is quadratic on the number of months elapsed since risk onset. Overall, comparing goodness of fit criteria across different specifications and the inclusion of calendar year dummies appears to provide the best fit.

The results suggest that the higher the (expected) generic price, the lower the delays of first generic adoption in individual markets. These findings were also robust to different definitions of expected generic price and to whether year dummies are present or excluded as shown by Table 2. Moreover, this finding was robust across a wide range of specifications, including our alternative modelling of the duration dependence as a semi-parametric specification (as defined above) and in the logistic specification. In both cases coefficient values were similar to those reported here. These other specifications are not reported for the sake of brevity.[12]

To illustrate our results, using our preferred price measure, defining the expected generic price as the average branded price of a molecule weighted by the median generic-branded price ratio in the local market, taking marginal effects and using an average (though skewed) price level of $21.13 per standard unit (SU) across

[12] Available as part of the on-line Appendix.

Table 3
Robustness check (marginal effects of regulatory impact derived from further definitions of expected price: cloglog with parametric time duration specification).

Variables	(5.1)	(5.2)	(5.3)	(5.4)	(5.5)	(5.6)	(5.7)
Generic price [log 5-year moving average branded price × (median generic-branded price ratio)]	0.150***			0.150***	0.129**	0.146***	
Generic price lagged 1 quarter		0.139***					
Log expected generic price [log branded price × (median generic-branded price ratio)]			0.146***				
Log expected generic price lagged 1 quarter							0.141***
Expected generic price defined as median generic-branded price ratio			−0.291				−0.067
Reference price dummy				0.161			
Generic substitution dummy					0.43		
Moving av. brand price (log of 5-year moving av. brand price) lagged over 4 quarters						0.012	
Expected market size (US $ sales)	0.132*	0.127*	0.130*	0.131*	0.122*	0.129*	0.129*
HHI (normalised)	0.647***	0.644***	0.646***	0.647***	0.650***	0.646***	0.645***
Molecule annual global sales (US $) (log)	−0.064	−0.064	−0.054	−0.062	−0.06	−0.062	−0.064
Years lag (log)	0.054	0.05	0.047	0.053	0.037	0.056	0.05
Global firm sales (log)	−0.003	−0.002	−0.006	−0.002	0	−0.002	−0.002
Duration dependence in years	0.018***	0.018***	0.018***	0.018***	0.019***	0.019***	0.018***
Duration dependence in years^2 (log)	−0.348***	−0.345***	−0.344***	−0.348***	−0.357***	−0.353***	−0.345***
ATC1 dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calendar year dummies	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of observations	19,698	19,809	19,827	19,698	18,560	19,698	19,809
Log likelihood	−2083.37	−2095.24	−2092.62	−2083.12	−1955.74	−2083.01	−2095.04
X^2	798.35	790.37	799.72	803.27	776.35	802.81	795.13

Note: Standard errors clustered at molecule-country level (standard errors in brackets). Duration dependence is specified as $t + \ln(t \times t)$, where t corresponds to months since risk onset.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

markets, we calculate that an increase of one standard deviation ($86.73 per SU) in expected generic prices increases the probability of launch by approximately 0.8%. Similarly, we find that an increase in branded prices of 1$ per SU increases the probability of launch by 0.8% (mean branded price was estimated to be $28.97 per SU).

Expected market size, defined as the product of the total molecule sales (in $s) in the relevant market prior to generic entry weighted by the average market share captured by generics for each country in each year, is significant across all specifications. Overall, an increase of one standard deviation in the expected generic market size reduced the delay of launch by 1.4–2.8%, depending on the specification. As shown by the HHI, competition appears to reduce the delay of launch. Generally molecule and firm characteristics show no statistical significance in any of our specifications.[13]

A semi-parametric analysis, including monthly fixed effects following the launch, replaces the assumption on the functional form of time to launch required in the parametric specification. This approach essentially assumes a constant probability of launch during each monthly interval. Parameter estimates were consistent with those reported in Table 2.[14]

4.2. Robustness checks

As well as the robustness checks carried out on the model specification itself, as referred to above, robustness checks were also carried out using a large number of different proxy variables for regulation, market size and firm and molecule characteristics. As in the main analysis, estimates were calculated with specifications across parametric and semi-parametric duration dependence, and for a logit specification. We present only parametric results with time trends, as the data suggested better overall fit when a parametric specification was chosen, and the parameter estimates were in any case robust to the various specifications.[15]

As a robustness check we have altered the definitions of expected generic price used as our main proxies for regulatory effect. We do so by using the log of the lagged expected generic price and the log of a moving average of (expected) generic prices over four quarters prior to launch, as well as the log of expected generic prices (ln_ExpPg) and median generic-branded price ratio (medRatioPgPb). We also interact generic price and time since onset of first generic launch. Further we replace the expected generic price with treatment dummies for the existence of reference pricing systems (RPS) and generic substitution (GenSubst) in individual countries.[16]

Regulatory dummy variables are also employed to control directly for the existence of a reference price system (RPS), to capture a situation where generic prices are referenced to branded product prices for each molecule, or to an international basket of generic product prices, and dummies are also used for countries where generic substitution, where pharmacists are allowed to substitute available generic products for branded products, is practiced. In Europe, about 70 per cent of countries use RPS to control

[13] Again other specifications are reported in the Appendix.
[14] Available as part of the on-line Appendix.
[15] All further results are available on request from the authors.
[16] We also check the correlation between our preferred price measure and all the other price measures, as well as with the various dummies used to indicate the presence of specific types of price regulation in individual countries RPS and generic substitution. When different price variables were regressed against our preferred price variable, the individual coefficients were always highly significant, indicating strong partial correlations. Simple correlations across these variables were 0.31–0.32 respectively, indicating that individual regulatory effects are positively (though moderately) correlated with our preferred price variable. Even so, as reported in the text, when regulatory fixed effects replaced our preferred measure there were no qualitative differences in the results (all results are available from the authors upon request).

the reimbursement level of medicines (Perry, 2006). The reference price for each molecule can be set at the price of the cheapest generic (e.g. Italy and Poland); at the median price of all medicines in the group (e.g. Netherlands); or at the highest price of available generic medicines (e.g. Portugal). A RPS is more successful in promoting generic use if the price difference between generics and branded drugs is high.

These robustness findings are presented in Table 3. Use of these further differentiated expected price variables again supports the hypothesis that the higher expected generic prices are the significantly lower is the delay of generic adoption, which we assume reflects more lax regulation in higher priced regimes. In addition, markets with higher branded product prices are associated with greater delays in the generic drug launch. This implies a possible regulatory trade-off between lowering branded prices, which improves static efficiency during the exclusivity period, but leads to delays in generic market entry, potentially jeopardising efficiency gains post-patent expiry. These findings are generally robust across all specifications, although only the cloglog parametric specification robustness results are reported here.[17]

Similarly, as with the RPS case, generic substitution is mandatory in some countries, whereas it is only promoted in others (e.g. by means of regressive margins on price), though incentives for substitution at the pharmacist level vary greatly across countries. Finally, substitution is not used at all in other countries. The impact of reference pricing schemes (RPS) and generic substitution was tested directly by variable dummies. While the signs on these were as the expected, indicating that reference pricing and generic substitution regulation increase generic launch times, the coefficients are generally not significant. This possibly reflects the fact that the indicator variables are necessarily crude attempts to capture the myriad of complex, heterogeneous regulations across (and within) countries. Moreover, given that these specific regulations do evolve over time, some of the effect will be captured in the time dummies. It is partly for this reason (the lack of specificity in the dummy variable definition), that we prefer the use of the various expected price variables in our analysis, as we believe they better reflect the impact of regulation on generic launch times.

None of these basic robustness checks alter the findings on our main variables of interest: expected generic prices, measured in various ways, remain statistically significant in explaining generic product launch times, with higher expected prices precipitating lower launch delays. Neither do the various robustness checks on the alternatively defined control variables alter the basic findings of our preferred specification and the expected influence of these variables.[18] Generally, the robustness checks support our underlying findings that for the 20 countries of interest, the larger the market size the lower the launch delay, and the greater the competition, the longer the delay.[19] The robustness checks also confirmed that molecule and firm characteristics tend to play little role in launch times.

5. Concluding remarks

This paper is one of the first to investigate how regulation affects the relative delay in the adoption of generic drugs across twenty national drug markets during 1999–2008. The main contribution of the paper is the incorporation of product-level price and volume information to analyse generic adoption in the decade 1999–2008, controlling for other influential factors, namely market competition, market size, and product and firm heterogeneity.

We find robust evidence that the higher are expected generic prices, which we argue incorporate expectations of regulatory impact, the lower is the time to launch of generics across the OECD. While we have little to say regarding the effectiveness of different, specific regulatory practices, it is clear that the lower the expected generic price, the longer the time to generic launch. Given the aggregated measure of expected price, it is clear that regulation might have an influence in two ways: directly through its effect on generic prices themselves or indirectly through a regulatory effect on the branded (patented) drug price. This latter effect is related to the potential regulatory trade-off involved with controlling branded product prices while trying to minimise the welfare loss associated with any detrimental impact on pharmaceutical R&D investment incentives. If this regulation of branded prices indirectly affects generic products and along with direct generic price regulation acts to reduce expected generic prices then, through our shown impact of delaying generic entry across markets, welfare is further reduced.

We also find strong evidence that expected generic market size is a significant determinant of launch, controlling for price, competition, firm and molecule characteristics. Expected levels of generic competition were also found to have a significant effect on generic launch strategies, with a highly fragmented therapeutic market reducing incentives for generic entry. The higher the Herfindahl-Hirschman Index, i.e. the smaller the concentration of generic firms, the lower is the delay into other markets from global launch. This is in contrast to the effect of competition in the patent-protected sector, where competition is found to incentivise entry (Kyle, 2007). This is to be expected, of course, as generics are commodity products with little room for differentiation and so they compete solely on price, while patent-protected products compete across quality- and product-differentiation. Importantly, we find that, while competition does affect generic market entry, molecule and firm characteristics do not.

Our major conclusion is that higher levels of regulation, through lowering the expected price to generic manufacturers, leads (ceteris paribus) to greater delays in generic entry in these countries. Given that this will have an impact on up-take of medicines this leads to a welfare loss. Further research could attempt to quantify this welfare loss in individual countries through estimation of price elasticity effects in individual markets.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhealeco.2014.04.004.

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[17] A large number of robustness tests were undertaken using different combinations of a number of definitions of our variables. In no case did the results conflict with the results of our primary analysis reported in Table 2. Again, further results are available through the on-line Appendix and a fully expanded set of robustness results are available on request from the authors.

[18] Once again all further results are available on request.

[19] Although, in a number of specifications where the a priori sign was of expected direction, the coefficient was insignificant.

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