



# The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s

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## Summary

We analyze the effect of price regulation on delays in launch of new drugs. Because a low price in one market may ‘spill-over’ to other markets, through parallel trade and external referencing, manufacturers may rationally prefer longer delay or non-launch to accepting a relatively low price. We analyze the launch in 25 major markets, including 14 EU countries, of 85 new chemical entities (NCEs) launched between 1994 and 1998. Each NCE’s expected price and market size in a country are estimated using lagged average price and market size of other drugs in the same (or related) therapeutic class. We estimate a Cox proportional hazard model of launch in each country, relative to first global launch.

Only 55% of the potential launches occur. The US leads with 73 launches, followed by Germany (66) and the UK (64). Only 13 NCEs are launched in Japan, 26 in Portugal and 28 in New Zealand. The results indicate that countries with lower expected prices or smaller expected market size have fewer launches and longer launch delays, controlling for per capita income and other country and firm characteristics. Controlling for expected price and volume, country effects for the likely parallel export countries are significantly negative. Copyright © 2004 John Wiley & Sons, Ltd.

**Keywords** new chemical entity (NCE); new drug launch; pharmaceutical price regulation; parallel trade; external reference pricing

## Introduction

The purpose of this study is to analyze the role of pharmaceutical price regulation as a contributor to delays in launch of new drugs. Launch delay, defined as months between the drug’s first global launch and launch in a specific country, varies significantly across countries. Delay in launch of new drugs may be costly to some consumers, if the new drug were cost effective relative to available

alternatives. Delay is also costly to the manufacturer because the drug’s patent continues to run regardless of whether the product is on the market.<sup>a</sup> Each day of delay can mean loss of revenues worth millions of dollars for high volume drugs, assuming the potential sales price exceeds marginal cost. Delays in launch of new drugs increased in the US following the 1962 Amendments to the Food, Drug and Cosmetics Act, which required that manufacturers show proof of efficacy in addition to safety and good

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manufacturing practices (GMP), before obtaining authorization to market a new drug, and other countries adopted similar measures. Several studies (for example [1]) documented the US 'drug lag,' relative to other industrialized countries in the 1970s, and Peltzman [2] estimated the costs and benefits of the increased delay following the new requirements for proof of efficacy.

In the 1990s, the US and the countries of the European Union (EU) adopted initiatives to accelerate the regulatory approval process. The US adopted user fees, which are paid by companies that submit drugs for regulatory review and are used to hire more reviewers. In 1995, the EU established the European Medicines Evaluation Agency (EMA), which offers a centralized EU-wide authorization process as an alternative to going through each country's own regulatory authority, as was previously required. A second alternative under the auspices of the EMA is the mutual recognition approach. Under mutual recognition, the originator firm submits the NCE for approval in one country and files for mutual recognition in other countries; once this rapporteur country has granted approval, the drug is automatically approved in the other countries unless they object within 90 days. The centralized procedure is required for biotechnology products (List A); it is optional for other products (List B) but more pharmaceutical manufacturers have chosen it in recent years. During the 1998–1999 period, 37 out of the total 52 new molecular entities were approved for market authorization in the EU countries through the EMA centralized procedure [3]. These measures have significantly reduced delays in authorization. The EMA centralized procedure reduced approval times to approximately 15 months [3]. Healy and Kaitin [4] report concordance of overall review time between the EMA centralized procedure and the US FDA.

In addition to proof of safety and efficacy, many countries also require that the manufacturer of a new drug obtain approval of the price and/or prior approval of eligibility for reimbursement through their health care systems. Most industrialized countries require such price/reimbursement approval, although details of the regulatory systems differ across countries. By contrast, the UK, the US and Germany do not require centralized price approval, although in the UK since April 1999 the reimbursement of some drugs has been subject to review by the National Institute of Clinical

Excellence (NICE). Thus the total delay can have several components: manufacturer delay in submitting the drug for market authorization; regulatory delay in obtaining authorization; manufacturer delay in submitting for price or reimbursement approval; regulatory delay in reaching agreement on reimbursement and price; and post-approval publication or listing delay, before the product can be reimbursed. Not all elements apply in all countries. As the authorization process has become more streamlined, delay in price and reimbursement approval may play a relatively more important role in overall launch delays.<sup>b</sup>

Previous studies have documented average launch delays for various countries and time periods, with most focus on the European Union (EU). Precise measures differ, depending on the countries under study, the time period, the sample of drugs and the measure of delay. Data on each of the separate components of delay are generally not available. The Boston Consulting Group [6] reports that countries with more regulation tend to get access to new drugs relatively later than those with fewer regulations. Greece, Belgium, and France (which regulate launch prices) had the longest average delay between drug approval and marketing (over 9 months), whereas Germany, the US, and the UK (which do not regulate launch prices) had the shortest average delay (less than 2 months). For the EU countries, Europe Economics [7] reports the average days from application for mutual recognition to award and the average days from application for price and reimbursement to award. In Belgium, France, Greece and Portugal, the delay in obtaining reimbursement approval was at least twice as long as the delay in market authorization. CMR International and Office of Health Economics [8] examined the country of first launch for new molecular entities and found a shift from Europe and Japan in the early 1990s toward predominantly the US in the late 1990s. The UK Pharmaceutical Industry Competitiveness Task Force [9] examined trends in total delay and post-authorization delay for new molecular entities in a selected group of countries in the early and late 1990s. For most countries, the lag between first world application and application in that country declined in the late 1990s, with Japan being the notable exception. The lag between application and approval also declined, but the decrease was minimal in Japan. The lag from approval to launch also generally decreased,

with France having the longest lag in both time periods.<sup>c</sup>

Companies have strong financial incentives to launch as early as possible, because the drug's patent continues to run regardless of whether the product is on the market. However, in recent years the growth of parallel trade in the EU and the tendency for countries to regulate their domestic prices based on prices in other countries (hereafter, external referencing) mean that a low price granted to one country may undermine the price the firm can obtain in another country [11–13]. The risk of price spillovers is expected to make companies more willing to delay launch or forego launch entirely in low-priced countries, particular in countries where potential sales volume is small.

All of the previous studies for the 1990s report simple mean lags for each country. None used multivariate analysis to distinguish effects of price levels from other country-specific characteristics, such as income per capita and potential for price spillovers due to external referencing and parallel trade, nor do they examine whether manufacturers trade off between price and delay and how this may vary by market size, by type of drug and characteristics of the firm(s) responsible for launch. Another limitation of previous studies is the failure to distinguish between potentially 'global' drugs, which can meet the strictest regulatory standards for safety and efficacy, and 'local' drugs that probably could not meet the strictest regulatory hurdles for efficacy in some countries. Many NCEs are local, that is, they are launched in only a few countries and are not submitted for approval in all major markets, in particular, not to the US FDA, the EU EMEA or the UK Medicines Evaluation Agency. Since the US and Europe are the largest potential markets, the failure to seek approval in these countries suggests that these compounds would probably not pass the stringent standards of efficacy set by these and other relatively strict regulatory authorities. Prior analyses that include these local compounds that do not have the potential for global launch could yield biased estimates of delay for the global compounds, if propensity to accept local compounds is correlated with low prices and other determinants of delay for global compounds. The availability of NCEs varied significantly across major markets in the 1990s. Of the total of 413 new molecular entities launched in the 1990s, the US had the greatest number launched (229) and only 35 were available in the seven

markets studied, specifically, the US, UK, Germany, Japan, France, Canada, and Australia [8]. Estimates of average delay in a country, based solely on the products that were launched in that country, may be biased because the resulting averages reflect different products and time periods in each country. A further source of potential bias is the treatment of censoring. Previous studies typically use the end of their study periods to calculate delays for not-yet-launched new drugs, which underestimates true differences in launch delay.

In this study, we focus on launch lags in 25 major markets for a sample of 85 potentially global compounds, defined as NCEs that were launched in the US or the UK for the outpatient market. Since these two countries are widely recognized as having relatively stringent standards for market authorization, drugs that enter at least one of these countries can be assumed to have potential for global launch. Our measure of launch in a country is first outpatient (retail) sales reported by IMS Health. We focus on the launch of new drugs in the outpatient or retail sector, because price regulation in most countries focuses on outpatient prices. Hospital prices are often negotiated between the manufacturer and the hospital, and launch is often earlier in the hospital sector. However, delay in obtaining regulatory approval of price and reimbursement for the outpatient sector is critical, because this sector accounts for roughly 80% of sales for most products in most countries. We use a Cox proportional hazard model to estimate the effect of expected price, expected volume and other factors on lags in launch and non-launch in the 25 major markets.

Our data do not distinguish between delay due to market authorization and delay in obtaining price/reimbursement approval. However, we also estimate the model for the 14 EU countries for the 29 NCEs that were approved through the EMEA centralized authorization procedure. For these NCEs, market authorization occurred simultaneously for all countries and hence the observed delays are purely related to price/reimbursement approval, including any post-approval delays. We do not measure price regulation directly, because the complexities of different countries' regulatory systems cannot be reduced to simple scalar measures. Rather, we use the country-specific average price of competitor drugs already on the market as a measure of the net effect of each

country's price regulation scheme. Hereafter we refer to lagged, average price of competitors as the ex ante expected price, since regulatory systems in many countries use prices of established products as a benchmark for setting prices of new products.

We find that the hazard of launch is significantly positively related to expected price. This result is robust to including country fixed effects and income per capita, which is a positive contributor to launch hazard. Launch hazard is also positively related to expected sales volume, consistent with the hypothesis that manufacturers rationally weigh foregone sales in their launch strategies. Controlling for expected price, market size and income per capita, some country effects are significant. We find similar results for the sample of EMEA-approved NCEs, with larger effects of price compared with the full sample of countries and NCEs. Significance levels are lower for the EMEA sample when we include country fixed effects, possibly due to the small sample of only 29 EMEA NCEs. These findings suggest that price regulation does contribute significantly to launch delay and that other country-specific factors also play a role. The similarity of results between the EMEA sample and the full sample suggests that the results for the full sample reflect primarily delay in price/reimbursement approval rather than market authorization.

## Theoretical framework

We hypothesize that the launch outcomes (occurrence and timing of launch) in a country reflect the interactions of the drug manufacturer and the government agencies in a two-stage process of market authorization and price/reimbursement negotiation. Depending on the country, the total launch delay can include delay in obtaining market authorization, which is required in all countries, and delay in negotiating a price or reimbursement level. Our interest is in the price/reimbursement delay, which is expected to add delay for countries that regulate prices.

The government in country  $j$  is assumed to have a reservation or maximum offer price. Under many prevailing regulatory systems, this maximum offer price is based on prices of existing products in the same therapeutic class, possibly with a mark-up if the new drug can demonstrate superior efficacy, safety, etc. More formally, if the government

estimates an incremental cost-effectiveness ratio (ICER) for a new drug relative an existing comparator drug, the maximum price at which the new drug  $i$  is cost-effective in country  $j$ ,  $P_{nij}^{\max}$ , can be written as

$$P_{nij}^{\max} = P_{oij} + (C_{nij} - C_{oij}) + k_j(Y_j)(E_{nij} - E_{oij}) \quad (1)$$

where  $P_{oij}$  is the price of comparator or existing drugs in country  $j$ ,  $(C_{nij} - C_{oij})$  is the difference in cost-offsets (for example, reduced hospital days) between the new drug and the existing drug,  $(E_{nij} - E_{oij})$  is the difference in efficacy,  $k_j(Y_j)$  is the ICER threshold used in country  $j$ , and subscripts  $n$  and  $o$  denote new and old, respectively. We assume that  $k$  depends on per capita income in the country,  $Y_j$ . Of course, at this maximum price the manufacturer would extract all social surplus from the new drug, so some bargaining down from this level is likely. Although most government regulatory systems informally consider cost-effectiveness relative to existing drugs as one factor in their reimbursement decisions, most consider other factors.<sup>d</sup> Nevertheless, to the extent that ICERs are considered, Equation (1) suggests that the government offer price for a given drug would vary across countries based on differences in the price of existing products, costs of other medical resources and differences in ICER thresholds, which are plausibly related to per capita income. Given this maximum offer price, a government may be willing to accept delay in launch, rather than accept a price that it considers unjustified or that would lead to expenditures in excess of its target drug budget. Concern for budgetary impact may lead to greater focus on drugs with relatively large potential volume,  $Q_{ij}$ . The government's offer price for product  $i$  in country  $j$ ,  $P_{nij}^{\text{offer}}$ , can thus be written as

$$P_{nij}^{\text{offer}} = g(P_{nij}^{\max}, Q_{ij}) \quad (2)$$

We assume that the firm seeks to maximize expected net revenue across all potential markets. If all markets are separable, the firm would rationally launch promptly in all markets and charge higher prices in countries with relatively high per capita income, assuming that income is either positively related to ICER thresholds and/or prices of existing products or that income is inversely related to price elasticity of demand. Other things equal, the firm would rationally accept a lower price in return for speedier market access. However, this strategy is less attractive if markets are not separable due to parallel trade and

external referencing. Thus if a firm accepts a low price in say France, it may not only undermine its future price in a not-yet-launched country, say, Italy, due to external reference pricing, but may also undermine its current higher price in, say, the UK, due to parallel exports from France. Consequently, it may be preferable to continue negotiations for a higher price in France, because the delay-induced loss of sales in France may be less than the revenue loss that would occur in other markets due to spill-over of a low price in France through parallel trade and external referencing. The opportunity cost of foregone sales due to launch delay is directly related to market size. This simple model implies that the firm's reservation or minimum ask price would fall within a relatively narrow band in all countries that are potentially connected. The firm's reservation or ask price in country  $j$ ,  $P_{nij}^{\text{Ask}}$ , can be written as

$$P_{nij}^{\text{Ask}} = f(Y_j, Q_{ij} | P_{nij}^{\text{Ask}} > P_{nij}^{\text{Min}}(X_i)) \quad (3)$$

where  $P_{nij}^{\text{Min}}$  is the reservation or floor price below which the firm will not launch in country  $j$ , and  $X_j$  denotes country  $j$ 's propensity for spillovers due to referencing and parallel exports. The firm may accept delay and, in the limit, forego launch entirely, rather than agree to a relatively low price in one country, particularly in a country that is small or is likely to become a source of parallel exports to other, potentially higher-price markets.

The trade-off between price and delay is expected to differ across markets and across products within markets. Countries in the EU are more exposed to spillovers than non-EU countries, because the EU explicitly permits parallel trade between EU member countries (but not from outside the EU) and several EU countries use external referencing formally or informally in their price regulatory process.<sup>c</sup> The parallel trade risk is also expected to be higher for high-volume products than for smaller volume products, assuming that the parallel trader incurs certain fixed costs of obtaining a licence, etc. The larger the potential volume, the greater the opportunity cost of delay for the firm but the greater the potential source of supply of parallel exports. Thus the net effect of market size on the firm's ask price is negative if the opportunity cost of foregone sales exceeds the expected revenue loss from parallel exports. Ideally, we would like to test for effects of growth of parallel trade directly by using difference-in-differences analysis applied to countries

that are significant parallel exporters vs those that are not. This is not possible because the parallel trade threat cannot be accurately measured and because price spillovers due to both parallel trade and external referencing were significant throughout our study period. We discuss below the role of parallel trade in observed differences across countries and perform a rough test for the effects of the EMEA, which reduced costs to parallel traders.

Bargaining results in launch of the product if the government's offer price equals or exceeds the firm's ask price,  $P_{nij}^{\text{Offer}} \geq P_{nij}^{\text{Ask}}$ . If this condition is not met,  $P_{nij}^{\text{Ask}} - P_{nij}^{\text{Offer}} > 0$  and the greater this difference, the longer the delay in launch. The hazard function of launch for product  $i$  in country  $j$  can thus be written as

$$h_{ij}(t) = h(P_{nij}^{\text{Ask}}(Y_j, Q_{ij}, X_j); P_{nij}^{\text{Offer}}(P_{oij}, Y_j, Q_{ij}); S, H) \quad (4)$$

where  $S$  denotes a firm's prior experience and  $H$  denotes the originator firm's home country status.<sup>f</sup> We hypothesize that the launch hazard will be greater for a firm with more negotiation experience or a firm that is launching in its home country. The efficacy differential ( $E_{in} - E_{io}$ ) is assumed to be similar across all countries. The cost offset differential ( $C_{in} - C_{io}$ ) is also expected to be similar across countries, except possibly due to differences in medical price levels which may be correlated with income.

Ideally we would estimate a full structural model, including equations for offer and ask prices, final approved price if any, and launch date. Given the limitations of our data, in this paper we estimate a reduced-form equation for the hazard (occurrence and delay) of launch, as a function of the determinants of the firm's ask price and the regulator's offer price. The reduced form hazard equation can be written as

$$h_{ij}(t) = h(P_{oij}, Q_{oij}, Y_j, X_j, S, H) \quad (3)$$

The launch hazard is expected to be positively related to the price of competitor products  $P_{oij}$  and to income  $Y_j$ ; the expected effect of volume  $Q_o$  is positive if the cost of foregone sales to the firm dominates its concern over spillovers and the regulator's concern over budget impact; launch hazard is expected to be inversely related to the potential for spillovers from that country,  $X_j$ . We

define  $P_{oij}$  and  $Q_{oij}$  as the quantity-weighted average price of competitor products and the number of standard units of competitor products in the same therapeutic class as the new drug to be launched, in Quarters 3 and 4 prior to the date of the drug's first launch in any country. Country fixed effects are included to control for spillover risk  $X_j$  and other country-specific factors in specifications that omit per capita income. If per capita income, operating via ICER thresholds (and possibly demand price elasticity and cost offsets of other medical services), were the only factor contributing to cross-national differences in drug prices, then the average price of competitor products would be insignificant after controlling for per capita income. To the extent that average price of competitor products is significant after controlling for per capita income, it provides a rough measure of the effect of price regulation net of per capita income. Hereafter we refer to the average price of competitor products as the firm's expected price.<sup>g</sup>

The indicator variable for whether the firm is launching in its country of domicile is expected to be positively associated with launch if either regulators tend to favor their domestic firms or if firms are more familiar with the regulatory process in their home country. A domestic firm may also anticipate more favorable market uptake of local products or political backlash from a delayed home launch. We use a firm's worldwide outpatient sales at the beginning of our study period to represent its global experience. This is expected to be positive if firms experience significant learning-by-doing and this experience increases their competence at managing the launch process. Since this variable is the same across all countries for a given firm, it captures the firm's internal experience with the launch process in general, not familiarity with a specific country's regulatory system.

This launch hazard equation is estimated using the Cox proportional hazard model, taking into account right censoring, that is, the fact that some products are not launched in some countries.

## Testable hypotheses

Since we lack information on the dates of application for, and approval of, market author-

ization and price/reimbursement approval, respectively, we cannot distinguish the delay caused by the authorization vs the price/reimbursement process, except within the EU countries for the sample of drugs that went through the EMEA centralized procedure. We also cannot distinguish delay due to government's administrative processes vs delay due to disagreement over the price. However, even if these dates were known, modeling these components of delay is complicated by endogeneity and interactions between the manufacturer and the government regulator. For example, in applying for market authorization, the manufacturer may initially put a low priority on countries expected to offer lower prices or requiring longer price/reimbursement negotiations. Within the EU, the pharmaceutical firm's choice of the EMEA centralized or mutual recognition procedure may depend on product characteristics, firm experience, and expected cross-market spillover effects from parallel trade and external reference pricing. Except for the subgroup of EU countries and the sample of new drugs approved through the EMEA centralized procedure, we only estimate how expected price and expected sales volume affect the combined regulatory and price/reimbursement delay. Specifically, this study tests the following hypotheses:

1. The lower the expected price, the longer the launch delay, controlling for product, firm, and country-specific factors, including income per capita. This would confirm that countries with lower prices face longer delays in launch.
2. The larger the potential unit sales volume, the shorter the launch delay. This would confirm that manufacturers are willing to trade-off price and volume (and this dominates any concern of regulators for greater budget impact of potentially high volume products).
3. Within the EU, the common parallel export countries experience longer launch delays, after controlling for expected price and expected sales volume and even for drugs approved through the EMEA centralized procedure. This would confirm that manufacturers are willing to delay launch in order to reduce the risk of parallel exports.

Two additional hypotheses related to effects of firm-specific experience are also tested:

4. *Ceteris paribus*, a firm with more global experience is predicted to have shorter launch delays.
5. *Ceteris paribus*, a firm is expected to launch earlier in its home country.

## Data and methodology

Our data are from two databases from IMS Health, a global market research company. IMS Drug Launches database (currently known as New Product Focus), hereafter called DL, reports new drug launches in 60 major markets of the world, with data on their NCE status, trade names, active ingredients, marketing companies, pack description, launch date, indication, therapeutic class, etc. We are interested in the launch experience of global NCEs in the 1990s in the retail markets of the 25 major markets that are listed in Table 3. We define a 'global' NCE as a NCE launched in either the UK or the US during the study period. The assumption is that manufacturers would seek to launch a NCE in either or both of these markets if the NCE could pass these countries' relatively stringent hurdles. Thus there is a strong presumption that NCEs that were launched in at least one of these markets could meet regulatory requirements of other markets. We focus on launch in the outpatient sector because this accounts for roughly 80% of total drug sales in most countries and because price regulation focuses on prices for the outpatient sector.

Using the DL database, we identified a total of 220 NCEs launched between October, 1994 and September, 1999. Of these, we excluded 80 NCEs because they were launched only in the hospital sector. An additional 45 NCEs were excluded due to no launch in the US or the UK. Finally, 10 NCEs that were first launched after October 1998 were excluded to allow a minimum observation period of 12 months for launch in other countries. Our final sample thus consists of 85 global NCEs that were first launched in the outpatient sector between October 1994 and October 1998. Of these, 29 NCEs were approved through the EMEA centralized procedure, including four biotech products (List A) for which approval through the centralized procedure is mandatory [15].

For these 85 NCEs, we extracted outpatient launch date (month/year) and other sales char-

acteristics from the IMS MIDAS database. MIDAS contains sales data on prescription drugs from country-specific audits of wholesalers and other sources. For each product in each country, MIDAS reports the molecule name, therapeutic class, international and local brand names, launch date, manufacturer(s), ex-manufacturer price, formulation, and sales volume for hospital and retail channels. We obtained MIDAS sales data for the 24 quarters between the fourth quarter of 1993 and the third quarter of 1999. We used sales data in Quarters 3 and 4 prior to a NCE's first launch date to estimate expected price and expected sales volume (see details in *Variable Definitions* below).

## Variable definitions

We define a NCE's global launch date as the earliest of country-specific launch dates in the 25 study countries' retail markets. This is likely to be the first retail launch worldwide, as these 25 countries include all the major pharmaceutical markets. A NCE's launch delay or lag in a country, conditional on an observed launch, is measured as the difference in months between the global launch date and the country-specific launch date. In the descriptive statistics table (Table 3), we report for each country both the number of NCEs launched in that country during the study period and the number of NCEs that were launched within 12 months of their respective global launch dates.

We use the IMS Anatomical Therapeutic Classification (ATC) system to categorize NCEs by therapeutic class.<sup>h</sup> We define a NCE's therapeutic class as its 3-digit ATC. The 3-digit ATC is usually a good proxy for a NCE's potential market, especially in the short run.<sup>i</sup> One notable exception is that the G4B class (other urological preparations) may underestimate potential sales for sildenafil (Viagra). Our 85 global NCEs represent 36 3-digit ATCs or therapeutic classes. For four NCEs that established a new 3-digit therapeutic class, we used a related 2- or 3-digit therapeutic class for calculating the expected prices and volume.<sup>j</sup> Data for five therapeutic classes were missing in Sweden or Norway, so we had a theoretical maximum of 2120 instead of 2125 potential launches for the 85 NCEs in the 25 countries. There are 1167 observed launches, indicating that approximately 45% of launches did not occur during the study period.

The MIDAS database reports the ex-manufacturer price, that is, the manufacturer's selling price to wholesalers. For each NCE, we defined its competitors' average price (hereafter expected price) in a country as the volume-weighted average price per standard unit (SU) for all products in its therapeutic class in Quarter 3 and Quarter 4 prior to its first global launch date. The IMS SU is defined as the smallest dose for each product form, for example, one tablet, one capsule, 5 ml of liquid, etc. To the extent that the mix of dosage forms in a therapeutic category differs across countries, this weighted average price may not be strictly comparable across countries but it should be representative of the expected dosage forms for that country. Moreover, the alternatives have similar or worse problems. Price per pack is more imprecise due to the significant differences in pack size across countries; another alternative is price per gram of active ingredient, but the distribution of price per gram, across dosage forms and across products within a therapeutic class, is even more skewed than price per standard unit, resulting in means that are highly sensitive to the sample selection. We used this expected price in the therapeutic category rather than the product-specific observed launch price for several reasons. First, price is an outcome of the launch negotiation and is determined simultaneously with launch delay. We lack the identifying variables necessary to estimate these two endogenous variables simultaneously. Second, the actual launch price is undefined for the 45% of launches that were not observed during our study period. In practice, for drugs that were launched, the expected price and observed launch price (conditional on launch) are significantly positively correlated, after log-transformations to reduce skewness and kurtosis (correlation ratio 0.353,  $p < 0.001$ ).<sup>k</sup>

The MIDAS data, which are usually based on audit of wholesaler invoices, are the best available data on ex-manufacturer drug prices. However, these data overestimate transactions prices in the US and the UK because they do not reflect off-invoice discounts. Specifically, the US price does not reflect off-invoice discounts given by manufacturers to managed care purchasers, Medicaid and other public purchasers. Similarly, the Midas data for UK prices may not accurately reflect discounts given to pharmacists by originator manufacturers to compete with parallel imports and generics. However, since these discounts in both countries are usually less in early years of the

product life-cycle, omitting these discounts should not lead to serious bias for our estimates of expected launch price. The IMS MIDAS database we acquired did not identify originator products. Therefore, we were unable to define expected price using only originator products, which might be a better measure of expected price for new launches. As countries with less price regulation tend to have more generic penetration [16], our measure of expected price may be an under-estimate in countries with relatively loose price regulation and strong generic penetration, notably the US, the UK, and Germany. To mitigate these problems, we include country indicators in some of the statistical models, which control for all country-specific factors including measurement error.

All prices in local currencies are converted to prices in UK sterling. We chose sterling as our base currency because the majority of study countries are European countries. The UK is a major parallel import market, hence the measure of other EU prices in terms of sterling is the most relevant measure for the purpose of considering the parallel import impact of accepting a particular launch price. All prices are inflated to December 1999 pounds, based on the UK wholesale price index.

As a measure of expected sales volume, we use sales in SUs in the therapeutic class in Quarters 3 and Quarter 4 prior to a NCE's first global launch date. For Sweden and Denmark, the MIDAS database only reports the combined hospital and retail sales. Therefore, our measured expected sales volume is biased upward in these two countries. The expected price may also be biased if there is a systematic difference in prices between the retail and hospital sectors in these countries. The presence of country indicators in some of our statistical models controls for any such bias.

NCEs that are launched in the originator firm's home country are identified by an indicator variable HOME. For recently merged companies, the HOME indicator is turned on for launches in both home countries. Finally, we measured a firm's global launch experience (SALES) using its worldwide outpatient sales in pounds sterling in Quarters 3 and 4 at the beginning of the study period.

In some models we include GDP per capita to control for per capita income differences. As the study countries' GDP per capita remained stable during our study period, we simply used the 1997



per capita GDP in US dollars.<sup>1</sup> Other countries' currencies were converted to dollars using 1997 currency exchange rates, rather than purchasing power parities (PPPs), because parallel trade is driven by cross-country price differences measured at prevailing exchange rates.

## Statistical model

We use the Cox proportional hazard model to simultaneously analyze the occurrence of launch of each NCE in each country and its launch lag, relative to that NCE's first launch date (hereafter called the global launch date) within our 25 countries. Launch lag is defined as number of months between a country-specific launch date and the global launch date, with right-censoring at the end of our study period. In the Cox model, the launch hazard for NCE  $i$  in country  $j$  at time  $t$  is the product of two factors:

$$h_{ij}(t) = \lambda_0(t) \exp\{\beta_1 x_{ij1} + \dots + \beta_s x_{ijs}\}$$

i.e. a baseline, unspecified, non-negative hazard function  $\lambda_0(t)$  and the exponential of a linear function with  $s$  covariates, including expected price, expected sales volume, etc. The Cox model is semi-parametric in the sense that it does not specify the baseline hazard function  $\lambda_0(t)$  and only estimates the  $\beta$  coefficients using the maximum partial likelihood method. Specifications of  $\lambda_0(t)$  lead to parametric proportional hazards models. For example, it becomes the Weibull model when  $\lambda_0(t) = t^\alpha$  (see, for example [17]). For estimation we use the PHREG procedure in SAS version 8.01 [18]. For an indicator variable with values of 1 and 0, the hazard ratio is the ratio of the estimated hazard for those with value 1 over the estimated hazard for those with a value of 0 (controlling for the other variables). For a continuous variable, subtracting 1.0 from the estimated hazard ratio and multiplying by 100 gives the per cent change in hazard for each one unit change in the explanatory variable.

The set of explanatory variables contributing to launch delay includes expected price, expected volume of units, SALES, HOME, therapeutic category indicators (1-digit ATCs), and country indicators (relative to the UK) or GDP per capita. Log transformations of expected price, expected volume, GDP per capita, and SALES are used under the assumption of decreasing (but positive) marginal effects.

Our key variables of interest, expected price and expected volume, are potentially correlated with the country indicators. We estimate three main Cox models, to test for separate effects of country characteristics, expected price and volume. First, the Country Comparison model includes only country indicators, SALES, and main therapeutic class (1-digit ATC) indicators. In this model, the country indicators reflect the combined effect of all country characteristics, including expected price, expected volume, per capita income, and all other country characteristics, including the price regulatory system and other factors affecting expected risks or returns, such as years of data protection or restoration of patent life for time spent in clinical trials or under regulatory review. The coefficients for the lower-price countries, including parallel export EU countries, are expected to be negative. The coefficient for SALES is expected to be positive, if experience increases a firm's productivity in bringing new drugs to market. Second, the Expected Price-Volume model includes expected price, expected volume, GDP per capita, SALES, HOME, and main therapeutic class indicators but excludes country fixed effects. In this model, the coefficients for expected price, expected volume, GDP per capita, and HOME are expected to be positive. Finally, we estimated the Full model with all explanatory variables except GDP per capita, which cannot be included with country fixed effects, due to collinearity. Including country and ATC fixed effects, the expected price and sales volume variables measure the within-therapeutic-class variation over time in the same country. The country indicators reflect country effects other than expected price and volume, such as GDP per capita, bureaucratic delays or country-specific propensities to be a base for parallel exports or for external referencing, or other factors affecting expected risks or returns beyond the pure price and market size effects.

As described earlier, since 1995 the EU has offered a choice of two alternative routes for market authorization – centralized procedure or mutual recognition.<sup>m</sup> The centralized procedure is required for biotechnology products (List A) and optional for other innovative drugs, but more pharmaceutical manufacturers have chosen it in recent years (List B). The centralized procedure is intended to accelerate the market authorization process, by granting a single EU-wide authorization. The mutual recognition approach gives a company the option of not seeking authorization

in certain markets, if it does not plan to launch in those markets. It may also be faster, depending on the rapporteur country selected and the backlog in each channel. Centralized authorization does not obviate the requirement to go through country-specific negotiations over price/reimbursement before retail launch in each country that requires such approval. Previous studies have documented the number of products going through each route but little is known about the factors that contribute to the choice of the centralized procedure. Anecdotally, it is hypothesized that the centralized procedure would increase exposure to parallel trade, because a common dosage form, pack size, labelling etc. are authorized for all EU countries. This eliminates the firm's ability to target different dosages to different countries, and reduces the parallel trader's costs associated with repackaging and providing labels in the language of the importing country.

We model the choice of the EMEA centralized procedure for the List B products using a logit model, with expected EU price, expected EU sales volume, and a NCE's rank in its therapeutic class during our study period as explanatory variables. The expected EU price and EU volume variables were defined as weighted averages over the price and volume in Quarters 3 and 4 prior to global launch, over all the 14 EU countries. Thus these variables are EU equivalents of the country-specific variables used in the country analysis. We defined a NCE rank indicator variable *FIRST* that takes the value 1 for the first molecule (by global launch date) in each therapeutic class, 0 otherwise. For the sample of 29 NCEs approved through the centralized procedure, we then estimate the three Cox hazard models. Although the sample size is small and non-randomly selected, the fact that they had the same delay in market authorization makes them an ideal sample to study the delay that is due solely to price and/or reimbursement negotiations in the EU countries.

As the study period ranges from October 1994 to September 1999, the observation period for launch in other countries after the first global launch of a NCE ranges from 12 to 60 months, with shorter observation periods for NCEs launched late in the study period. Such right censoring applies to all countries so should not induce bias across countries, but does differ across NCEs. We test the robustness of our findings using two alternative specifications. The first is to stratify the Cox model by the 85 NCEs, hereafter

called the NCE Fixed Effect model. This is equivalent to assuming a different baseline hazard function for each NCE. The main drawback is that the effect of all NCE-specific factors that are invariant across countries such as SALES, are embedded in the baseline hazard functions and not separately estimated. This NCE Fixed Effect Cox model is used to test the robustness of our findings on 3 main variables – expected price, expected volume, and HOME. The second specification estimates a logit model with launch of a NCE within 12 months after its first global launch date as the dependent variable. This logit model does not incur the unequal right censoring across NCEs but does not take into account launch differences within 12 months or launches after 12 months.

## Results

### NCE, firm, and country characteristics

Table 1 lists the distribution of the 85 global NCEs by therapeutic class and the number in each class that were approved through the EMEA centralized procedure. The highest number of NCEs ( $n = 19$ ) was for central nervous system, followed by systemic anti-infectives ( $n = 12$ ) and alimentary tract ( $n = 10$ ). The gynecological, urological system and sex hormones had the lowest number of NCEs ( $n = 2$ ). Among the main therapeutic classes, the unweighted average expected price for each NCE-country combination is highest in J (systemic anti-infectives) and lowest in R (respiratory system); the unweighted average expected market size for each NCE-country combination is highest in C (cardiovascular system) and lowest in L (oncology). The high standard deviations for expected price and expected market size are due to significant country variations, especially in expected market size.

Table 2 lists the distribution of firms by number of NCEs launched during the study period. A total of 42 pharmaceutical or biotechnology firms were involved in launching the 85 global NCEs. When 2 or more firms were associated with a NCE, we designated as the originator the firm responsible for the first launch; if two firms launched simultaneously or as a joint venture, we assigned originator status to both firms. About half of the firms ( $n = 20$ ) only launched 1 NCE during the

Table 1. Distribution of 85 NCEs and 25 EMEA-approved NCEs by main therapeutic class (1-digit ATC)

ATC	Name	All NCEs	EMEA NCEs	Expected price (All NCEs)		Expected volume (All NCEs)	
				Mean	STD	Mean	STD
A	Alimentary tract	10	3	0.162	0.181	140691	282265
B	Blood and blood forming organs	5	2	0.148	0.194	68629	81249
C	Cardiovascular system	9	1	0.322	0.146	233334	355877
D	Dermatologicals	5	2	0.642	0.858	67047	204639
G	Gynecological, urological system and sex hormones	2	1	0.216	0.142	128316	240878
J	Systemic anti-Infectives	12	8	1.207	0.670	18383	49070
L	Oncology	9	4	0.712	0.489	9471	19111
M	Musculo-skeletal system	4	1	0.716	0.527	82120	235307
N	Central nervous system	19	5	0.218	0.384	84217	170205
R	Respiratory system	4	0	0.129	0.096	221560	331555
S	Sensory organs	6	2	0.487	0.285	21670	56813
Total		85	29	0.474	0.567	90715	216489

Table 2. Distribution of firms by number of NCEs launched

NCEs	Number of firms	SALES (million UK pounds)	
		Mean	STD
1	20 <sup>a</sup>	396	333
2	11	815	546
3	4	777	540
4	3	1189	891
6	3	1039	555
7	1	1280	Not relevant
Total	42 <sup>b</sup>	738	563

<sup>a</sup>Including 4 firms with zero sales; only 16 firms used in mean and STD calculation.

<sup>b</sup>Including 4 firms with zero sales; only 38 firms used in mean and STD calculation.

study period, and the highest number of NCEs launched by one firm is 7. The average SALES (for 6 months) for these firms was 738 million UK pounds, with a standard deviation of 563 million UK pounds, excluding 4 firms with zero reported SALES at the beginning of our study period. Baseline SALES is positively associated with number of NCEs launched in our study period, which is unsurprising.

Characteristics of the 25 study countries are summarized in Table 3. None of the countries had

all the 85 NCEs launched during the study period. The three countries that do not require price approval before launch had the most launches: the US led with 73 launches, followed by Germany ( $n = 66$ ) and the UK ( $n = 64$ ). At the other extreme, only 13 NCEs were launched in Japan, followed by Portugal ( $n = 26$ ) and New Zealand ( $n = 28$ ). Figure 1 gives the Kaplan–Meier estimates of cumulative launch probability over a 30-month period from the first launch date in any country. The US consistently has the highest launch probability, reaching an 80% launch probability in 14 months and 86% in 30 months. Japan has the lowest launch probability, reaching on 7% in 14 months and 11% in 30 months. Countries with fewer launches also tend to have a longer average launch delay for those NCEs that are launched (Figure 2 and Table 3), and fewer NCEs launched within 12 months of the global launch date (Table 3). The US, the UK, and Germany had the shortest average launch delays and the highest number of launches within 12 months, while Japan and Portugal had the longest average launch delays and were among the 3 countries with the lowest number of launches within 12 months. Average launch delay (for NCEs launched) ranged from 4.2 months for the US to 23.5 months for Japan. US-based firms launched or co-launched 36 NCEs, followed by the UK ( $n = 12$ ), Switzerland ( $n = 10$ ), and Germany ( $n = 9$ ) (Table 3).

Table 3. Country characteristics for 85 global NCEs

	GDP per capita <sup>a</sup>	Launched NCEs	Launch delay (month)			Launched in 12 months	HOME	Expected price			Expected volume			Expected price rank			Expected volume rank		
			Mean	STD	Max			Mean	STD	Max	Mean	STD	Max	Mean	STD	Max	Mean	STD	Max
AUSTRALIA	22,649	43	14.1	7.6	17	0	0.377	0.418	58063	70201	16	2	25	11	4	20			
AUSTRIA	25,520	54	12.4	9.4	31	0	0.540	0.641	22179	26904	13	1	22	16	10	25			
BELGIUM	23,922	41	18.2	7.6	8	0	0.525	0.541	27298	27544	9	1	21	15	9	25			
CANADA	20,800	56	12.2	7.8	28	0	0.462	0.413	73840	84062	11	2	24	8	4	18			
CZECH	5,146	31	21.4	9.7	6	0	0.202	0.250	25748	36590	23	4	25	18	8	24			
GERMANY	31,982	62	11.8	8.9	39	3	0.557	0.539	14603	14938	9	1	25	18	10	25			
FINLAND	23,700	66	8.8	8.7	50	10	0.538	0.574	268216	320052	11	1	23	3	1	9			
FRANCE	23,736	57	11.6	8.4	37	1	0.568	0.587	15158	17856	10	1	21	20	12	25			
FRANCE	24,227	45	14.9	9.1	19	7	0.347	0.338	228560	224945	15	2	25	3	1	11			
GREECE	11,524	45	18.6	10.1	10	0	0.421	0.427	22089	27713	15	2	25	16	10	22			
HOLLAND	24,146	48	10.2	8.3	34	0	0.583	0.594	35733	38902	8	1	20	13	6	23			
IRELAND	21,798	44	10.0	8.6	30	0	0.420	0.464	7165	9711	15	8	23	24	15	25			
ITALY	20,348	44	17.2	9.3	13	1	0.345	0.293	134928	167211	18	1	24	5	2	12			
JAPAN	34,206	13	23.5	16.7	4	4	0.969	1.157	234705	378785	3	1	25	5	1	24			
MEXICO	4,271	45	14.8	9.4	19	0	0.248	0.263	43998	57491	21	3	25	13	2	25			
NEW ZEALAND	17,229	28	13.4	6.6	11	0	0.501	0.643	9730	14548	14	1	24	22	14	25			
NORWAY	35,194	47	15.5	8.7	17	0	0.562	0.564	12217	13371	10	1	23	21	15	25			
POLAND	3,721	31	20.5	7.9	3	0	0.075	0.065	84969	120081	25	5	25	9	1	22			
PORTUGAL	10,659	26	22.1	11.0	4	0	0.335	0.321	32869	44744	18	5	24	14	9	24			
SOUTH AFRICA	3,661	38	14.4	6.8	12	0	0.409	0.383	11639	22264	12	2	24	23	9	25			
SPAIN	14,249	49	15.7	8.0	16	0	0.403	0.484	107530	111375	18	6	25	7	3	12			
SWEDEN	27,007	62	7.8	7.1	45	8	0.626	0.818	35979	49392	13	1	25	12	6	25			
SWITZERLAND	36,117	56	9.7	8.0	36	14	0.681	0.677	16831	19262	3	1	22	18	5	25			
USA	30,368	73	4.2	7.4	65	38	0.681	0.488	538194	596543	3	1	24	1	1	13			
UK	22,373	64	7.2	8.3	53	12	0.473	0.574	180293	266268	16	2	24	6	1	16			
Total		1168	12.8	9.6	607	98	0.474	0.567	90715	216489									

<sup>a</sup> 1997 GDP per capita in US \$.

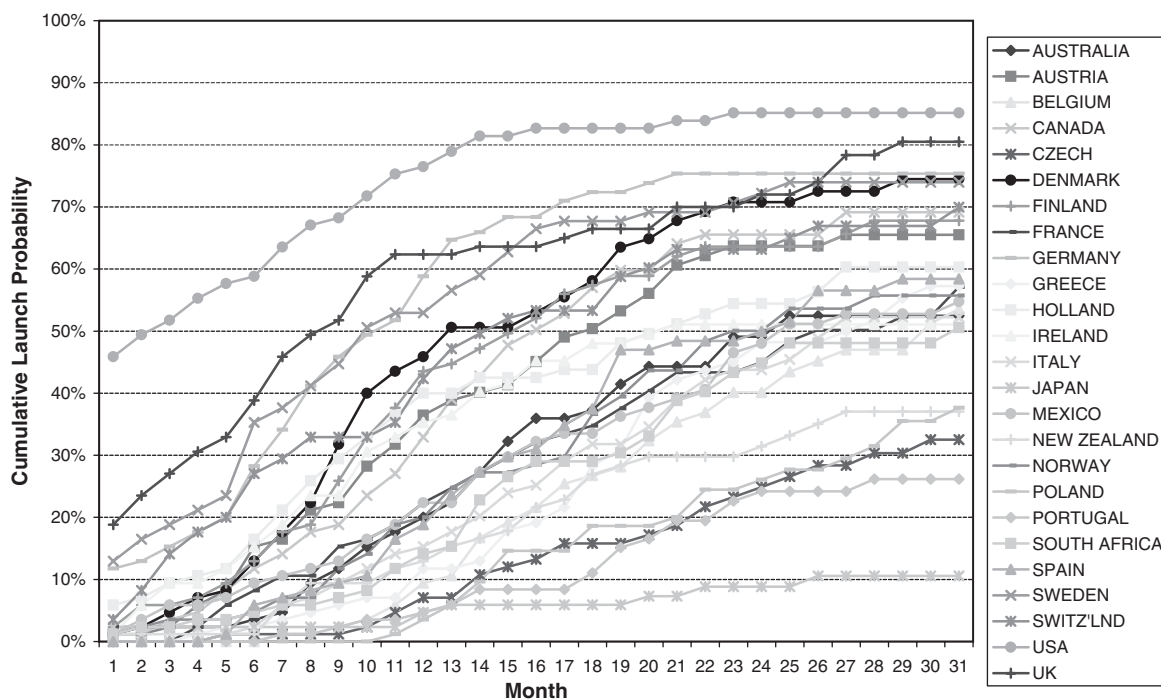


Figure 1. Kaplan–Meier estimates of cumulative launch probabilities by month

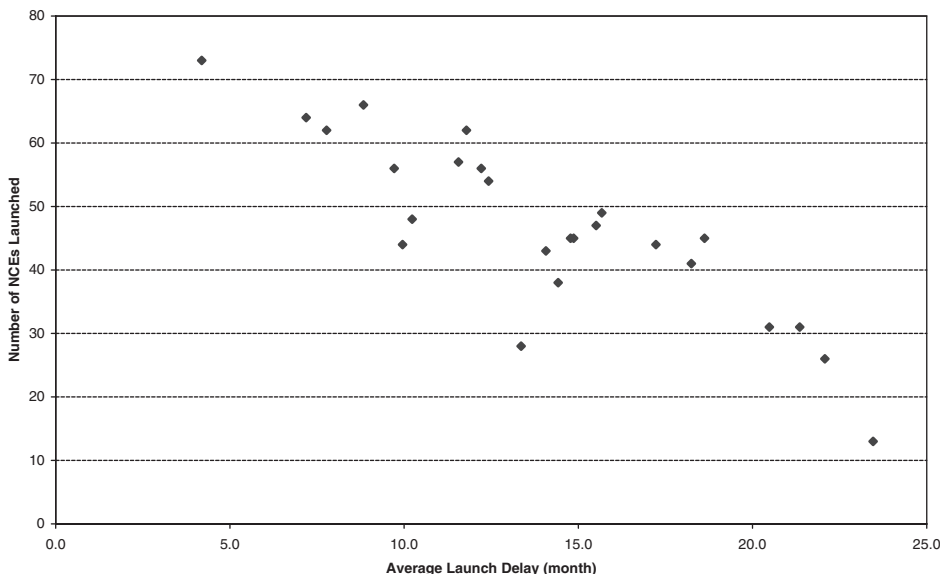


Figure 2. Number of NCEs launched and average launch delay, by country

Figures 3–5 plot the relationship between number of launches, average expected price, and GDP per capita for each country. Average

expected price is positively correlated with GDP per capita (Figure 3) and both expected price and GDP per capita are positively correlated with

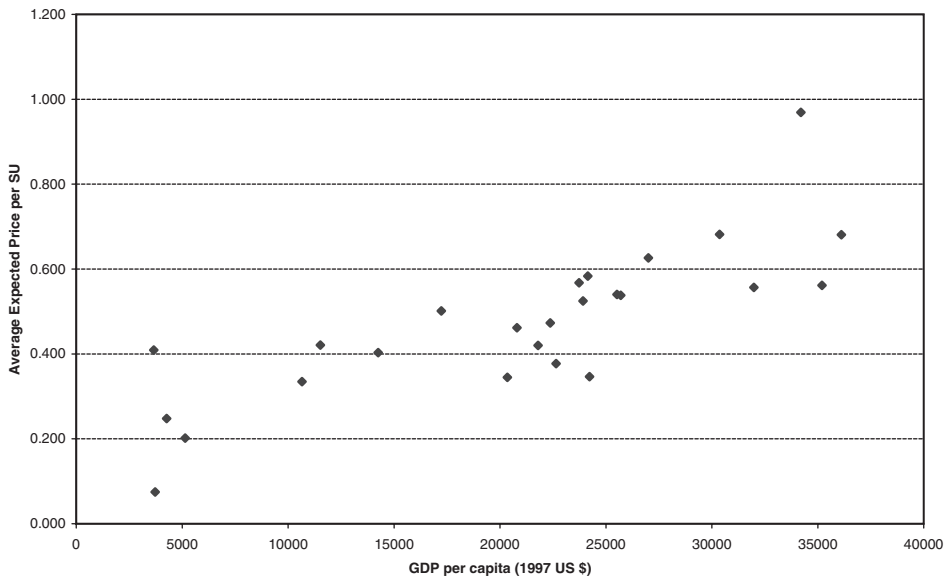


Figure 3. Average expected price and GDP per capita, by country

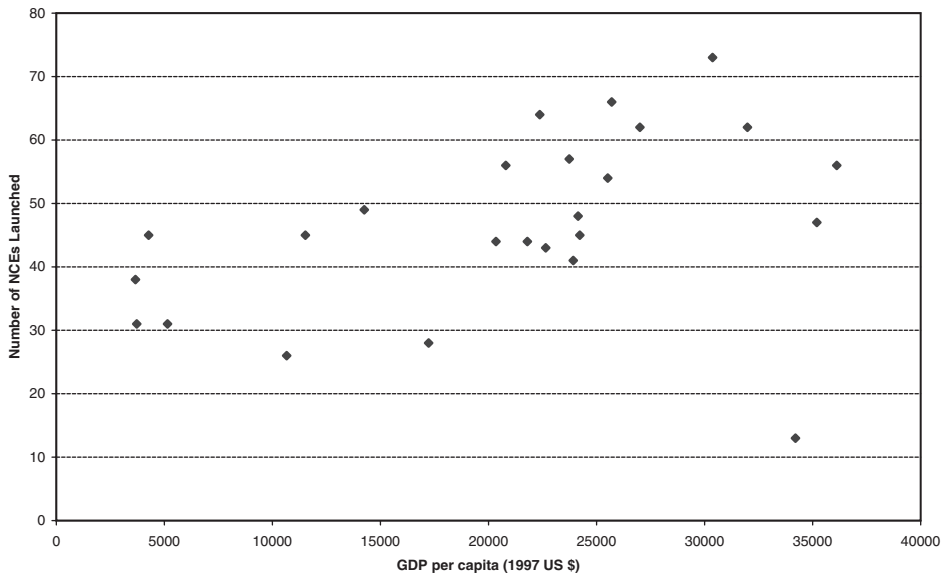


Figure 4. Number of NCEs launched and GDP per capita, by country

number of launches. Japan is a major outlier, with few launches despite a relatively high GDP per capita and average expected price. Germany and the UK rank 2nd and 4th in number of launches but only 10th and 13th in price. There is an over-

13-fold difference between countries in average expected price, but the difference is less than 5-fold if Poland is excluded. Recall that our measure of expected price is a volume-weighted average of prices of all products in the therapeutic category,

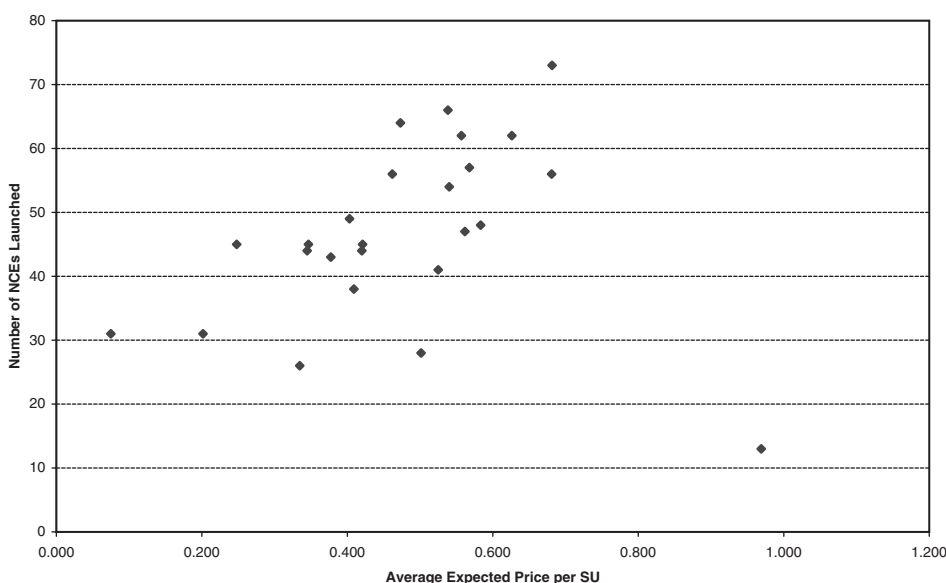


Figure 5. Number of NCEs launched and average expected price, by country

including generics. Thus the observed differences across countries in expected prices reflect differences in the range of product and dosage forms and their relative weights in utilization within the class, in addition to price differences for specific products. In particular, our expected price measure may be downward biased as an estimate of expected prices for originator products in countries with large generic market shares, such as Germany, the UK and the US. Japan and Poland are at the extremes of the price distribution but both have long launch delays and few launches, suggesting that factors beyond price also play a role in observed launch lags. In Japan, regulatory delays related to market authorization, including the requirement that clinical trials be done in Japan, are an unusually important contributor to delay [9]. By contrast, in Poland a low expected price that is below the firm's minimum ask price is more likely the dominant factor. The distribution of average expected volume (unweighted across the 85 NCEs) is even more skewed than for average expected price (Table 3). It should be noted that these cross-country differences in expected price and volume vary significantly across therapeutic classes. For example, for the 36 therapeutic classes, the US's rank in expected price ranges from 1 to 24 (median = 3); Poland's rank ranges from 5 to 25 (median = 25).

### Cox regressions

Results from the Country Comparison model (Table 4) confirm the simple statistics in Table 3, showing that there are statistically significant differences among the 25 markets in access to new drugs. Compared with the UK, Japan had the most negative coefficient (hazard ratio = 0.068), followed by Portugal (hazard ratio = 0.152) and New Zealand (hazard ratio = 0.181), all with  $p < 0.0001$ . There are significant differences across several therapeutic classes, with gynecological, urological system and sex hormones (G) and cardiovascular system (C) having relatively shorter delays. Since the cardiovascular category has the highest expected sales volume, its effect is consistent with the hypothesis that manufacturers are less willing to accept delay when foregone sales are large. On the other hand, there are only 2 NCEs in the gynecological, urological system and sex hormone category, one of which is sildenafil (Viagra). Viagra may have biased the estimated G class effect as it was launched without reimbursement in some countries. These ATC effects remain significant after controlling for expected price and volume.

The coefficients for the common explanatory variables present in both the Expected Price-Volume model (with or without GDP per capita)

Table 4. Cox model results on the launch of 85 global NCEs in 25 countries

Variable name	Country comparison model			Expected Price-Volume model			Expected Price-Volume model (with GDP)			Full model			NCE fixed effect model		
	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio
Log (expected price)				0.235***	0.035	1.265	0.157***	0.039	1.170	0.217***	0.047	1.242	0.236***	0.042	1.267
Log (expected volume)				0.093***	0.020	1.098	0.066**	0.020	1.069	0.138***	0.035	1.148	0.063**	0.022	1.065
Log (SALES)	0.207***	0.024	1.230	0.170***	0.023	1.186	0.173***	0.023	1.189	0.202***	0.024	1.224	0.168***	0.024	1.214
HOME				1.248***	0.116	3.483	1.193***	0.116	3.299	0.762***	0.127	2.142	1.681***	0.131	5.368
Log (GDP per capita)							0.226	0.053	1.254						
<i>Country indicators</i>															
AUSTRALIA	-1.156***	0.198	0.315												
AUSTRIA	-0.684***	0.185	0.504												
BELGIUM	-1.286***	0.201	0.276												
CANADA	-0.676***	0.184	0.509												
CZECH	-1.652***	0.220	0.192												
DENMARK	-0.380	0.179	0.684												
GERMANY	-0.094	0.176	0.910												
FINLAND	-0.517**	0.183	0.596												
FRANCE	-1.069***	0.195	0.343												
GREECE	-1.187***	0.195	0.305												
HOLLAND	-0.801**	0.192	0.449												
IRELAND	-0.929**	0.196	0.395												
ITALY	-1.171***	0.196	0.310												
JAPAN	-2.688***	0.305	0.068												
MEXICO	-1.080***	0.195	0.340												
NEW ZEALAND	-1.707***	0.228	0.181												
NORWAY	-0.968**	0.193	0.380												
POLAND	-1.691***	0.220	0.184												
PORTUGAL	-1.884***	0.233	0.152												
SOUTH AFRICA	-1.337***	0.206	0.263												
SPAIN	-1.141***	0.190	0.368												
SWEDEN	-0.152	0.180	0.859												
SWITZERLAND	-0.535**	0.184	0.585												
USA	0.400*	0.173	1.492												
<i>I-dieit</i>															
<i>ATC indicators</i>															
A	-0.28*	0.131	0.756	0.076	0.150	1.079	-0.033	0.153	0.968	-0.121	0.157	0.886			
B	-0.528**	0.176	0.590	-0.114**	0.191	0.892	-0.233**	0.195	0.792	-0.212	0.202	0.809			
C	0.433**	0.116	1.542	0.387**	0.132	1.472	0.366**	0.132	1.442	0.301	0.146	1.352			
D	-0.102	0.150	0.903	0.242	0.156	1.274	0.143	0.159	1.153	0.191	0.162	1.210			
G	1.141***	0.175	3.130	1.271***	0.187	3.566	1.204***	0.188	3.333	1.243***	0.191	3.465			
L	-0.037	0.121	0.964	0.156	0.122	1.169	0.100	0.123	1.105	0.163	0.125	1.177			
M	0.049	0.164	1.050	0.231	0.165	1.259	0.181	0.165	1.199	0.194	0.166	1.214			
N	0.236*	0.100	1.266	0.495***	0.123	1.640	0.392**	0.126	1.480	0.372	0.129	1.451			
R	0.204	0.145	1.226	0.432**	0.168	1.540	0.333*	0.169	1.395	0.231	0.177	1.260			
S	0.078	0.138	1.081	0.255	0.141	1.290	0.176	0.142	1.192	0.253	0.144	1.288			
Chi-square (DF)				316 (14)			335 (15)			624 (38)			193 (3)		

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



and the Full model (Table 4) are very similar. Both expected price and expected volume have a significant positive effect on the hazard of launch, i.e. reducing launch delay, with a larger effect for expected price than for volume. In the Expected Price-Volume model without controlling for GDP per capita, a 10% increase in expected price or expected volume is associated, respectively, with a 2.65% or 0.98% increase in launch hazard (both  $p < 0.0001$ ). Figure 6 shows the simulated effects of changes in Log (Price) from its mean value to  $\pm 2$  standard deviations (SDs) on cumulative launch probability over 30 months. Parameters are based on estimates from the Expected Price-Volume model without controlling for GDP per capita, with the other co-variables set to their mean values. After 12 months, i.e. in the 13th month, the cumulative launch probabilities are 50.0% (Mean + 2SDs), 32.5% (Mean), and 19.9% (Mean - 2SDs) respectively. Controlling for GDP per capita in the Expected Price-Volume model reduces the effects of expected price and market size but their coefficients remain highly significant (Table 4).<sup>n</sup>

In all models a firm's global launch experience (SALES) and its home country (HOME) are both positive contributors to early launch, consistent with the hypothesis that launch experience in general and in the home country in particular is valuable in reducing launch delay.

Adding the country indicators in the Full model leaves the coefficients for expected price and expected volume essentially unchanged. This tends to confirm that launch decisions are influenced by expected price and sales volume, not simply by general characteristics of each country's regulatory and market environment. Several of the country indicator variables are significantly negative relative to the UK (the omitted country) and their hazard ratios are often larger in the Full model. Since the Full model controls for expected price and volume, the country indicators presumably reflect other country-specific factors including GDP per capita, bureaucratic delays, or expected cross-market spillover effects such as propensity for parallel exports and external reference pricing, over and above the related effects that are associated with low expected price. Japan continues to have the most negative hazard ratio, followed by Portugal and New Zealand. Within the EU, the six countries with the most negative coefficients are Portugal, Italy, France, Belgium, Spain, and Greece. These are all countries with strict price controls and are likely major parallel export countries due to lower prices. To test whether delays in these parallel exporting countries increased following the introduction of the EMEA in 1995, which facilitated parallel trade by accelerating EU-wide market authorization with standardized formulations, labelling, etc., we

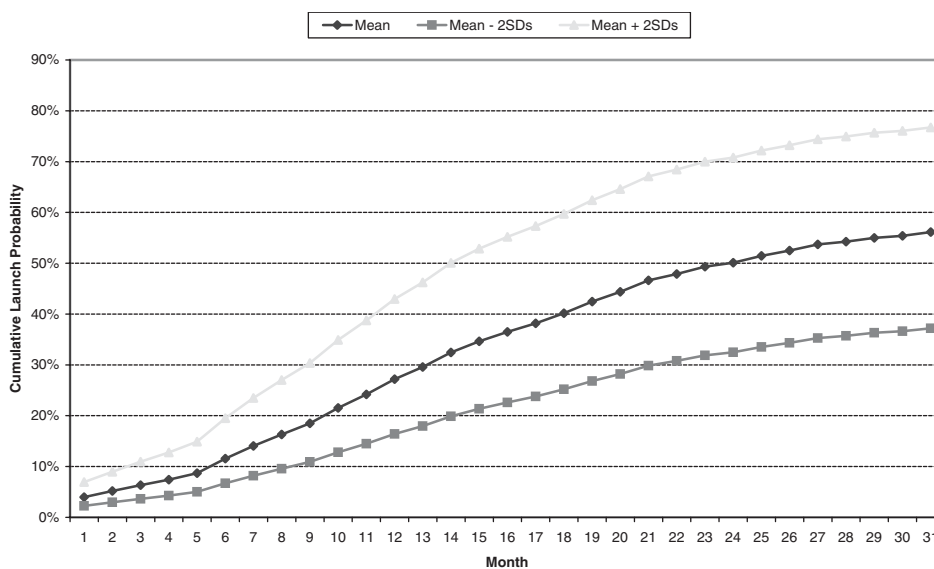


Figure 6. Predicted cumulative launch probabilities for different log-transformed price values based on the expected Price-Volume model (without GDP per capita)

created an indicator variable for NCEs first launched after October 1996, the midpoint of our study period. We tested its interaction with the above country indicators but found no evidence of longer country-specific delay effects after October 1996. However, our sample size of NCEs launched before the EMEA may be too small to observe significant effects. Moreover, since our measure reflects the combined delay of market authorization and price/reimbursement approval through launch, the hypothesized increase in price/reimbursement delay in the EMEA period may be offset by more rapid market authorization by the EMEA.

To test whether a firm is willing to accept a lower price in larger markets such as France, we tested the interaction between expected price and expected volume but this interaction was not significant at conventional levels. This could reflect the offsetting considerations, that while markets with larger expected volume have higher opportunity cost of delay, larger markets may also pose a greater threat of parallel exports, at least for EU countries.

The two alternative specifications, the NCE Fixed Effect Cox model (Table 4) and the logit model for launch within 12 months (not reported due to space limitations), further validate the findings on expected price, expected volume and HOME.

### EU subgroup analysis

Table 1 shows that the distribution of NCEs approved through the EMEA centralized procedure, by therapeutic class, differs from the distribution of the full sample of 85 NCEs. For example, 8 of the 12 NCEs in the systemic anti-infective class, including all HIV-AIDS drugs, were approved through the centralized procedure, while only 1 out of the 9 cardiovascular NCEs used the centralized procedure. The HIV-AIDS products faced strong political pressure for rapid launch in all countries, which may have contributed to the choice of the centralized procedure.

Table 5 summarizes the launch experience of the 29 NCEs that were approved through the EMEA centralized procedure, in each of the 14 EU countries. The three countries with the most launches are Sweden ( $n = 23$ ), Denmark ( $n = 22$ ), and Germany ( $n = 21$ ); the four countries with the fewest launches are Portugal ( $n = 5$ ), Italy ( $n = 8$ ),

Greece ( $n = 12$ ), and Spain ( $n = 12$ ). Thus approval through the centralized procedure is no guarantee of prompt launch in all countries. These delays and failure to launch can be attributed unambiguously to the price/reimbursement system and related publication delays. Average launch delay (for NCEs launched) ranges from 8.1 months for Germany to 17.4 months for Belgium (which has an unusually long publication delay [19]); however average delay is not as strongly correlated with number of launches as in the full sample. Among the 14 EU countries, France, Italy, and Portugal have the lowest average expected prices, deviating significantly from the other countries, while Germany, France, and Italy have the highest average expected volume. It should be noted that, similar to the full sample in Table 3, a country's rank in expected price and expected volume vary significantly across therapeutic classes (see Table 5).

The Cox analysis for NCEs launched through the EMEA centralized procedure is reported in Table 6. Recall that for this subgroup variation in launch dates should reflect solely the influence of price/reimbursement factors, since market authorization occurred simultaneously through the EMEA. In the Expected Price-Volume models with or without GDP per capita, the effect of expected price is greater for the EMEA subgroup (hazard ratio 1.662,  $p < 0.01$ , Table 6) than for the full sample (hazard ratio 1.265,  $p < 0.001$ , Table 4). Similar to the full sample results (Table 4), controlling for GDP per capita leads to a smaller but still highly significant coefficient for expected price in the EMEA/EU sample (Table 6). Interestingly, the effect of GDP per capita is much larger in the EMEA/EU sample than in the full sample (hazard ratio 5.109 vs 1.254, both  $p < 0.001$ ), suggesting that GDP per capita has a larger impact on launch hazard within than outside the EU.<sup>o</sup> This may be due to the fact that price spillovers from parallel trade (and possibly external reference pricing) are more prevalent within the EU. In other words, low-income may be associated with a larger price spillover effect through parallel trade and external referencing for EU countries than for non-EU countries. In the Full model, the coefficient and hazard ratio for expected price are similar in the EMEA subgroup and the full sample but significance is lower in the EMEA sample, possibly due to the small sample size. Expected volume does not have a significant effect on launch in the EMEA sample. Except for

Table 5. EU country characteristics for 29 EMEA-approved NCEs

COUNTRY	Launched NCEs	Launch delay		Launched in 12 months	HOME	Expected price			Expected volume			Expected price rank			Expected volume rank		
		Mean	STD			Mean	STD	Mean	STD	Mean	STD	Median	Min	Max	Median	Min	Max
AUSTRIA	14	8.6	4.8	11	0	0.810	0.761	16499	22023	4	1	14	10	5	13		
BELGIUM	15	17.4	8.6	4	0	0.749	0.678	16499	18073	5	1	14	9	5	12		
DENMARK	22	10.6	5.9	15	1	0.702	0.587	10417	11888	6	1	14	11	6	13		
GERMANY	21	8.1	5.1	17	2	0.747	0.649	210742	313212	7	1	14	1	1	4		
FINLAND	18	9.7	6.0	13	1	0.755	0.680	9487	13219	6	1	11	12	8	14		
FRANCE	13	14.2	8.9	5	3	0.384	0.342	175803	219496	12	1	14	2	1	5		
GREECE	12	15.8	7.2	4	0	0.615	0.511	13031	22028	9	1	14	12	6	13		
HOLLAND	16	9.1	7.0	12	0	0.799	0.747	22973	31546	4	1	12	7	4	13		
IRELAND	13	8.1	5.3	9	0	0.630	0.565	3312	4679	8	3	13	14	11	14		
ITALY	8	15.3	7.8	3	0	0.417	0.338	93560	130862	11	2	14	3	1	5		
PORTUGAL	5	10.4	4.6	4	0	0.474	0.376	23189	42905	12	2	14	9	6	14		
SPAIN	12	12.5	7.2	6	0	0.662	0.645	70140	95433	10	3	14	5	2	6		
SWEDEN	23	10.1	5.9	14	1	0.770	0.727	22337	26527	10	1	13	6	4	14		
UK	19	8.4	6.4	15	1	0.764	0.733	71606	94340	7	1	14	4	1	9		
Total	211	10.9	7.0	132	9	0.663	0.619	54525	130136								

Table 6. Cox model results on the launch of 29 EMEA-approved NCEs

Model	Country comparison model			Expected Price-Volume model			Expected Price-Volume model (with GDP)			Full model			NCE fixed effect model		
	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio	Coefficient	SE	Hazard ratio
Log (expected price)				0.508**	0.161	1.662	0.380*	0.156	1.463	0.244	0.169	1.277	0.421*	0.200	1.524
Log (expected volume)				0.013	0.058	1.013	-0.013	0.056	0.987	-0.102	0.110	0.903	0.059	0.061	1.061
Log (SALES)	0.073	0.039	1.076	0.069	0.039	1.072	0.079*	0.039	1.082	0.091*	0.040	1.095	0.289	0.367	0.749
HOME				0.466	0.357	1.594	0.200	0.356	1.222	-0.289	0.367	0.749	0.851*	0.389	2.342
Log (GDP per capita)							1.631***	0.280	5.109						
<i>Country indicators</i>															
AUSTRIA	-1.010**	0.371	0.364												
BELGIUM	-1.202**	0.350	0.301												
DENMARK	0.047	0.316	1.048												
GERMANY	0.344	0.318	1.410												
FINLAND	-0.394	0.340	0.674												
FRANCE	-1.154***	0.363	0.315												
GREECE	-1.420***	0.372	0.242												
HOLLAND	-0.368*	0.341	0.692												
IRELAND	-0.822**	0.362	0.440												
ITALY	-1.846***	0.424	0.158												
PORTUGAL	-2.353***	0.506	0.095												
SPAIN	-1.271**	0.372	0.280												
SWEDEN	0.245	0.314	1.277												
<i>I-digi ATC indicators</i>															
A	1.430***	0.274	4.178	2.542***	0.489	12.709	2.342***	0.482	10.402	2.390***	0.502	10.918			
B	0.421	0.335	1.523	1.567**	0.482	4.794	1.456**	0.521	4.290	1.413*	0.557	4.108			
C	2.257***	0.354	9.557	2.601***	0.390	13.483	2.389***	0.384	10.908	2.925***	0.491	18.631			
D	-0.665	0.384	0.514	-0.141	0.390	0.868	-0.300	0.395	0.741	-0.553	0.428	0.575			
G	2.703***	0.337	14.920	3.313***	0.405	27.463	3.233***	0.402	25.364	3.289***	0.421	26.816			
L	-0.455***	0.305	0.635	-0.191**	0.306	0.826	-0.295***	0.307	0.745	-0.344	0.313	0.709			
M	1.627***	0.340	5.086	1.522**	0.339	4.583	1.567***	0.339	4.794	1.701***	0.346	5.478			
N	1.452***	0.205	4.271	2.284***	0.393	9.815	2.116***	0.382	8.298	2.253***	0.403	9.513			
S	-14.930	416.2	0.000	-14.205	451.8	0.000	-14.046	370.246	0.000	-14.538	424.2	0.000			
Chi-square (DF)	277 (23)			193 (13)			233 (14)			284 (26)			10.4 (3)		

Table 7. Logit model results on the choice of EMEA centralized procedure

Variable	Full model			Reduced model		
	Coefficient	SE	<i>P</i> value	Coefficient	SE	<i>P</i> value
Intercept	4.644	3.289	0.158	5.268	2.504	0.035
FIRST	-1.884	0.604	0.002	-1.902	0.602	0.002
Log (expected EU volume)	-0.340	0.278	0.221	-0.399	0.188	0.034
Log (expected EU price)	0.122	0.423	0.774			
Chi-square (DF)	16.6 (3)		0.001	16.6 (2)		0.0003

France, the same list of countries, i.e. Portugal, Italy, Greece, Belgium and Spain, have the most negative country effects on launch, controlling for expected price and volume (all  $p \leq 0.001$ ). Thus these findings in the Full model appear to be attributable to the price/reimbursement systems in these countries, not to their market authorization systems. Among the 29 NCEs, four (2 in therapeutic class S, 1 in D, and 1 in L) were not launched in any EU countries during the study period. The estimates were unaffected by exclusion of these NCEs. The NCE Fixed Effect Cox model (Table 6) and the logit sensitivity analyses confirmed these findings.

Finally, we examined the determinants of the choice of centralized procedure. We have a total of 80 products with global launch dates after January 1, 1996, which in theory might have used the centralized procedure. Of these, 29 (or 36%) used the centralized procedure; for 4 biotech products the choice was mandatory and these 4 are excluded from the analysis. Our theoretical model implies that firms are less likely to use the centralized procedure for NCEs that are most exposed to parallel trade, since the simultaneous approval of uniform dosage forms in all countries increases the likelihood of parallel trade by reducing traders' costs of repackaging and labeling. In Table 7, we report the results of logit estimates for the sample of 76 products launched after 1996. In the reduced model (with expected EU price removed), expected EU volume and FIRST (being the first drug in its therapeutic class during our study period) are significantly negatively related to choice of the centralized procedure. Not shown in Table 7, the global launch date of a NCE was not significant and was removed from the logit model. The negative effect of expected EU volume is consistent with the hypothesis that large potential market size and hence high risk of parallel trade discourages

use of the centralized procedure. The negative effect for first in class is surprising, since initially the EMEA was intended to focus on innovative drugs. It is possible that the observed negative effect of being first in class may also reflect an expected volume effect, since first-in-class drugs often have a first mover advantage and retain relatively large sales, compared with follower products, for several years after launch. Thus first-in-class products may be more at risk for parallel trade than follower products. First-in-class products may also be more at risk of price spillovers through regulation based on external referencing, because for first-in-class products there are no similar products already on the market that could serve as an internal benchmark for regulating price. Thus if first-in-class products are more at risk, relative to follower products, of cross-national price spillovers due to both parallel trade and external referencing, this could lead manufacturers of first-in-class products to choose the mutual recognition procedure rather than the centralized procedure, because mutual recognition may permit more flexibility for varying formulations, launch dates and other strategies that reduce the risk of cross-national price spillovers. These conclusions are tentative because the sample is small and is drawn from the start-up phase of the EMEA.

## Discussion

This study of launch lags for 85 new, globally important drugs in the 25 major markets during the mid-late 1990s finds significant variation across countries in both the number of drugs launched and the mean delay from the first global launch. The number of NCEs launched ranges from 73 in

the US, with a mean lag of 4.2 months, to 13 in Japan, with a mean lag of 23.5 months. There is a strong correlation between number of launches and average launch delay (conditional on launch). Large variation also exists within the European Union and even for products that are approved through the centralized procedure, which receive market authorization simultaneously in all countries. Of the 29 EMEA-approved NCEs since 1996, 23 were launched in Sweden, compared to only 5 in Portugal, 8 in Italy and 12 in Greece and Spain during our study period.

Countries that have lower expected prices tend to have fewer products launched and longer delays for those products that are launched, after controlling for per capita income. This finding tends to confirm the hypothesis that price regulation negatively affects the timing and occurrence of launch. The magnitude of the expected price effect is similar in the EMEA sample and the full sample. Since all launch variation in the EMEA sample can be attributed to delays associated with price-reimbursement regulation, it seems safe to infer that the expected price effect that we observe in the full sample does in fact reflect launch delays that are due to price/reimbursement regulation rather than market authorization. The exception to this conclusion is Japan, which experienced extremes of delay and non-launch despite relatively high prices. Thus in Japan manufacturer reluctance to launch appears to be less important than regulatory delays in market authorization and price approval.

These findings are also broadly consistent with the hypothesis that price spillovers, due to parallel trade and external referencing, negatively affect launch of new drugs. If markets were perfectly separable (no price spillovers), there would be no reason for firms to delay or withhold launch in low-price countries, as long as prices offered exceed marginal cost plus fixed costs of launch. However, the existence of price spillovers creates incentives for firms to delay or withhold launch in countries that have low prices. Thus to the extent that prices are correlated with income, permitting parallel trade within the EU would tend to reduce access to new drugs in low-income EU countries. Pharmaceutical price regulation that reduces prices below the level expected based on a country's per capita income exacerbates this problem and may extend launch delays even to some relatively high income countries, such as France and Belgium.

Consistent with this, controlling for expected price, countries that have strict regulation and have traditionally been major parallel exporters (Portugal, Italy, France, Belgium, Spain, and Greece) also have negative country fixed effects. These presumably reflect delays due to expected parallel trade, external referencing and other bureaucratic effects, beyond the pure price regulatory effect. These country effects persist after controlling for the country of domicile of the launching firm. Thus the tendency for earlier and more numerous launches in the US, the UK and Germany does not simply reflect the fact that firms from these countries were disproportionately the originators of the drugs that were launched.

Controlling for expected price and country fixed effects or per capita income, larger markets have shorter launch delays. This is consistent with the hypothesis that manufacturers weigh the opportunity costs of launch delay and that their incentive for prompt launch of potentially high volume products dominates any incentive of regulators to delay the launch of high volume products that could have disproportionate budget impact. Finally, firms with more global launch experience, as measured by worldwide outpatient sales at the start of our period, have shorter launch delays, presumably reflecting the advantages of experience and/or multinational operations with local subsidiaries in most major markets and possibly multi-country trial data to support their launch applications in different countries.

One limitation of this study is the lack of data to separate out the authorization delay from the price/reimbursement delay and, within the price/reimbursement delay, the component that is due strictly to the administrative process versus the component that is related to disagreement over the price. The availability of such data might shed light on the sequential game underlying new drug price and launch decisions. Another limitation is that we did not test the effect of delay on actual launch prices, specifically, whether manufacturers that delay launch in lower-price countries get higher prices in return. Our measure of expected price may reflect factors other than regulation; however, our results are robust to including income as a control variable, country indicators to control for other country-specific factors and therapeutic category indicators. Thus it seems plausible that our expected price variable is indeed capturing differences in regulation.

This analysis provides important evidence on the effects of pharmaceutical price regulation on delays in launch and non-launch of new drugs, and suggestive evidence of the effects of price spillovers due to parallel trade and external referencing. A full evaluation of such policies would require information on the effect of such launch delays on use of other medical services, on the direct and indirect costs of medical care, on other restrictions on access to new drugs and on health outcomes. *Ceteris paribus*, the foregone health benefits to patients from delay in launch are presumably greater for NCEs that are more innovative, in terms of providing either new therapies or significantly improved therapies. To the extent that delay reflects real uncertainty as to whether the new drug is cost-effective and the appropriate price, given the norms and budgets of each country's health care system, then there is some benefit if delay helps resolve these issues, to offset against the cost in foregone benefits to patients. To the extent that delay reflects rational strategies by manufacturers to avoid price spillovers from low price countries, analysis of the costs and benefits of price regulation and, in particular, parallel importing and external referencing, must consider not only effects in the home country but also spillover effects in terms of foregone access in other countries.

This study was funded by AstraZeneca Pharmaceuticals. Y. Richard Wang is an employee of AstraZeneca Pharmaceuticals.

## Acknowledgements

We wish to thank Emilio Lois of APIFARMA [10] for provision of its survey results and Lisa Croll for administrative assistance. We also thank participants at the 4th European Health Economics Conference and the 2003 American Economic Association annual meeting and two anonymous reviewers at this journal for helpful comments.

## Notes

- a. Under the Uruguay round of GATT, countries that are members of the WTO grant 20 years of patent life, from the date the patent is filed. For pharmaceuticals, the patent is typically filed before the drug enters clinical trials, which may take 5–12 years. To (partially) make up for this loss of patent life due to the regulatory requirements of market authorization, some countries grant some patent term extension, e.g. the 1984 US Waxman Hatch Act and the 1992 EU Supplemental Protection Certificate regulation for medicinal products grant up to five years patent extension. However, such patent term extensions are based on delay in market authorization, not delay in obtaining price/reimbursement approval.
- b. According to the *Financial Times* [5], Plans to speed up drugs approvals in the European Union could be a useful pick-me-up for pharmaceutical companies. ... But the EU's centralized approvals procedure is already relatively efficient. The problem is that national authorities subsequently set prices and decide on including drugs in the reimbursable list for their healthcare systems. The key to speeding drugs to market lies in accelerating this second tier.
- c. The Portuguese industry association (APIFARMA) regularly surveys time taken to achieve marketing, price, and reimbursement approvals in Portugal, by authorization route used. For brand name products, the mutual recognition route had the shortest average delay to marketing approval (180 days vs 452 days for centralized procedure and 441 days for national) and the national route had the shortest average reimbursement approval time (153 days vs 213 days for centralized procedure and 298 days for mutual recognition) between January 1998 and March 2001 [10].
- d. During the time period of our data, CE was formally required in Australia and Canada, and informally required in the UK through NICE since April 1999, near the end of our data.
- e. The leading parallel export countries in the EU include Belgium, France, Greece, Italy, Portugal, and Spain [14]. The EU countries that use external reference pricing include Denmark (since April 1997, up to 10 EU countries excluding Greece and Italy), Greece (lowest in the EU), Ireland (lower of UK or the average in Denmark, France, Germany, the Netherlands, and the UK), Italy (average of up to 12 EU countries, must be on market for 4 countries and at least 2 with direct price controls), the Netherlands (since June 1996, average price in Belgium, France, Germany, and the UK), and Portugal (lowest in France, Italy, and Spain) [14].
- f. Subscripts for firm are omitted for simplicity.
- g. Launch delay is expected to be inversely related to the price observed in our data (and launch hazard is positively related to the observed price) because the observed price is the price of competitor products prior to launch of the new NCE. As shown in Equation (1), this can plausibly be interpreted as the regulator's offer price and as the expected price under a regulatory regime, in the absence of significant differential cost offsets or superior efficacy

- for the new drug compared to existing drugs. The theory predicts that launch delay would be positively related to the firm's ask price; however, we do not observe the ask price or any reasonable proxy for it, so we cannot test this hypothesis.
- h. The IMS ATC system, which is similar to the WHO ATC system, classifies drugs by body system (alimentary, cardiovascular, etc.), clinical indication, and mechanism of action. There are up to four levels within the ATC system but many therapeutic classes have only three levels.
  - i. For example, C8A represents calcium channel blockers; C9A represents angiotensin converting enzyme inhibitors; C10A represents cholesterol/triglyceride reduction agents such as statins.
  - j. These therapeutic classes (and their proxies) are C9C (C9), J5C (J5), N7D (N7), and R3J (R3D).
  - k. Both distributions are highly skewed and not normal, especially that of observed launch prices. Although log-transformations reduce skewness and kurtosis for both distributions, the Kolmogorov–Smirnov goodness-of-fit tests reject the null hypotheses of log-normal distributions.
  - l. We chose not to convert GDP per capita to 2000 UK pounds as GDP per capita is usually reported in US \$. This will not affect the coefficient estimates beyond a factor of proportionality.
  - m. Using individual national systems is a third possibility but is unlikely to be a desirable alternative for potentially global NCEs.
  - n. Note that the income coefficient in the Expected Price-Volume specification may reflect other country-specific factors that are correlated with income, so is not as pure income effect.
  - o. When we re-estimated the Expected Price-Volume model using all 85 NCEs for the 14 EU countries, the coefficients for expected price and market size are similar to the full sample of 25 countries but the coefficient for GDP per capita remains larger (hazard ratio 2.638,  $p < 0.001$ ). In addition, removing the major outlier Japan from the full sample leads to a similar estimate for GDP per capita (hazard ratio 1.374,  $p < 0.001$ ).
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