

The Impact of Price Regulation on the Launch Delay of New Drugs – A Study of Twenty-Five Major Markets in the Late 1990s

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Abstract

Question: This study analyzes the effect of pharmaceutical price regulation on the launch of new drugs. Obtaining regulatory approval for a price may entail administrative delay. In addition, since 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 of drugs to accepting a relatively low price, particularly for high-volume drugs that would be targets for parallel trade. However, the manufacturer’s opportunity cost of launch delay is greater, the larger the drug’s potential sales. We use IMS data to examine the effects of expected price, expected market size, country indicators, and other factors on new drug launch.

Data/Methods: To focus on drugs with potentially global markets, we limit the sample to new chemical entities (NCEs) launched in the UK or US outpatient market between October, 1994 and October, 1998. There are 85 such NCEs, representing 36 therapeutic classes. The 25 countries represent the major pharmaceutical markets, including 14 EU countries. Each NCE’s expected price and market size in each country are estimated using lagged price per unit and lagged market size of competitor drugs in the same (or related) therapeutic class in Quarter 3 and Quarter 4 prior to its first worldwide launch. In addition to expected price and volume, other explanatory variables include: home country of the launch firm, a firm’s total sales at the beginning of our study period, main therapeutic class indicators, and country indicators. We use the Cox proportional hazard model to analyze the effects of these variables on the delay or non-occurrence of launch, relative to the first launch in any country. We also test for effects of the accelerated authorization procedure introduced by the European Medicines Evaluation Agency (EMA) in 1995.

Results: There are 1,167 observed launches during our study period, or about 55% of the potential maximum. 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. Countries that have fewer launches tend to have a longer average launch lag. Expected price and market size have a significantly positive effect on launch probability (both $p < 0.001$), i.e. both reducing launch delay, with a larger effect for expected price. Characteristics of the originator firm, specifically, launch in its home country and its global experience, are also significant. Controlling for expected price and volume, some country effects are still significant: Japan is most negative (Hazard Ratio 0.071), followed by Portugal (Hazard Ratio 0.156) and New Zealand (Hazard Ratio 0.185). Within the EU, the likely parallel export countries have the longest delays. We find no evidence that this effect increased with the EMEA; however, this conclusion is tentative because of the small sample (29) of drugs approved through the EMEA centralized procedure. These findings are robust to alternative sample design, NCE-stratified Cox analysis, and logit analysis.

Conclusions: Our results suggest that countries with lower prices or smaller market size experience longer delays in access to new drugs. Other country-specific effects are also significant, controlling for price and volume. Whether such delays affect health outcomes for consumers, utilization of other medical services and total health expenditures is not addressed here.

Introduction

The purpose of this study is to analyze the role of pharmaceutical price regulation as a contributor to delays in new drug launch. Delay in launch of new drugs is costly to consumers, who forego the benefits of the new drug. It is also costly to manufacturers, because the drug's patent continues to run regardless of whether the product is on the market.¹ Thus each day of delay is a day of on-patent revenues foregone, which can be worth millions of dollars for high volume drugs. 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 manufacturing practices (GMP), before obtaining authorization to market the drug, and other countries adopted similar measures. Several studies in the 1970s and 1980s documented the US "drug lag," relative to other industrialized countries.²

¹ Under the Uruguay round of GATT, countries that are signatories to GATT 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 US Waxman Hatch Act and the EU Supplemental Protection Certificate 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.

² For example, Peltzman (1973), Wardell (1973), Wardell and Lasagna (1975), and Grabowski, Vernon, and Thomas (1978) measured 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. Since its inception in 1995, the centralized procedure was required for biotechnology products (List A); it is optional for other products (List B) but more pharmaceutical manufacturers have chosen it in recent years. These measures have significantly reduced delays in authorization. The EMA centralized procedure reduced approval times to approximately 15 months (CMR International, 2001), and drug manufacturers are increasingly using the EMA centralized procedure.

In addition to proof of safety and efficacy, many countries also require that the manufacturer of a new drug obtain approval of the price as a condition of reimbursement through their health care systems. Most industrialized countries require such price/reimbursement approval, although details of the regulatory system differ across countries. The main exceptions are the UK, the US, and Germany, although in the UK towards the end of our period reimbursement for some drugs was increasingly subject to advisory 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, delay in submitting for price or reimbursement approval, and delay in obtaining price or reimbursement approval. Not all elements apply in all countries.

Previous studies have documented average launch delays for various countries and time periods, with recent focus mainly 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 (1999) reports that countries with more regulation tend to get access to new drugs relatively later than those with fewer regulations. Greece, Belgium, and France had the longest average delay between drug approval and marketing (over 9 months), whereas Germany, the US, and the UK had the shortest average delay (less than 2 months). For the EU countries, Europe Economics (1999) reports the average days from application for mutual recognition to award and the average days from application(s) for price and reimbursement to award(s). In Belgium, France, Greece and Portugal, the delay in obtaining reimbursement approval was at least twice as long as the delay in market authorization. The Portuguese

industry association (APIFARMA) regularly surveys time taken to achieve marketing/price/reimbursement approvals in Portugal and reports significant differences based on the authorization route used – EMEA centralized procedure, mutual recognition or national. For brand products, the mutual recognition route had the shortest average marketing approval time and the national route had the shortest average reimbursement approval time during 1998-2001. During the 1998-1999 period, 37 out of the total 52 new molecule entities were approved for market authorization in the EU countries through the EMEA centralized procedure (CMR International, 2001). CMR International (2000) 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 as country of first launch in the late 1990s. Healy and Kaitin (1999) report concordance of overall review time between the EMEA centralized procedure and the US FDA. For some markets, notably Japan, delays in market authorization appear to have increased.

As the authorization process becomes more streamlined, price and reimbursement negotiations may play a relatively more important role in recent launch delays. According to The Lex Column in *Financial Times* (A fine balance: Pharmaceuticals. July 19, 2001), “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.” Figure 1 shows trends in total delay and post-authorization delay in the early and late 1990s as reported by the UK Pharmaceutical Industry Competition Task Force (2001, originally Figure 4.1 in the report).

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 (Danzon, 1997, 1998; Huttin, 1999). 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.

Evidence on the causes of delay is sparse. None of the studies for the 1990s has used multivariate analysis to test for effects of price regulation and other characteristics of the country, the drug or the firm(s) responsible for launch, nor do they examine how manufacturers trade off between price and delay and how this may vary by market size. Another limitation of previous studies is the lack of focus on important, potentially global new drugs. The total number of NCEs launched worldwide includes many that are not submitted for approval in all countries, in particular, not in the FDA, the EMEA and the UK Medicines Evaluation Agency. Since the US and Europe are large 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. Including in the analysis these compounds that do not have the potential for global launch could bias estimates of the determinants of delay for the global compounds. The availability of NCEs varied significantly across major markets in the 1990s. There were a total of 413 new molecular entities, with the highest number launched in the US (229) but only 35 were available in all of the 7 major markets (US, UK, Germany, Japan, France, Canada, and Australia). (CMR International, 1999)

Previous studies may be subject to further bias by their treatment of censoring or non-launch in some countries. Estimates of average delay in a country, based solely on the products that were launched in that country, may be biased because the products that were launched are not a random sample and because the resulting averages reflect different products and time periods in each country. Or, previous studies typically use the end of their study periods to calculate delays for not-yet-launched new drugs. These limitations may lead to underestimation of the true differences in launch delay.

In this study, we focus on a sample of 85 potentially global compounds, defined as NCEs that were launched in the US or the UK outpatient market. Since these 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. We use a Cox proportional hazard model to estimate the effect of expected price, expected volume and other factors on lags in launch in 25 major markets. We test for differences between the 14 EU countries and the other countries. Our data do not distinguish between lags in market authorization and lags in price approval. However, we do test for differential effects among the 14 EU countries for the 29 NCEs that went through the EMEA centralized authorization procedure. For these NCEs, market authorization occurred simultaneously for all countries, hence the observed delays are purely related to price/reimbursement approval.

We find that launch is significantly positively related to expected price, with or without country fixed effects, and some of the country effects are significant. This suggests that price regulation does contribute significantly to launch delay, and that other country-specific factors also play a role. Launch delay is negatively related to the NCE's expected sales volume, consistent with the hypothesis that manufacturers rationally weigh foregone sales in their launch strategies. We find similar results for the sample of EMEA-approved NCEs, with larger effects of price, although significance levels are lower for the EMEA sample when we include country fixed effects, possibly due to the small sample of EMEA NCEs. The similarity of results between the EMEA sample and the full sample suggests that the results for the full sample reflect primarily delay in the price/reimbursement approval process rather than market authorization.

Theoretical Model

We hypothesize that the launch outcomes (price and date) reflect the interactions of the drug manufacturer and the government agencies in a two-stage process of market authorization and price/reimbursement negotiation. In general, the government is 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 for drug spending. The concern for budgetary impact leads to greater focus on drugs with relatively large potential sales. The objective of the firm is to get prompt market access at a profit-maximizing price. While the firm may traditionally have accepted a lower price in return for speedier market access, particularly in large markets such as France, this strategy is less attractive with the breakdown of market separability due to parallel trade and external referencing. Thus if a firm accepts a low price in say France, it will not only undermine its future price in a not-yet-launched country, say, Italy, due to external reference pricing, but 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. This simple model implies that firms would attempt to price within a relatively narrow band throughout the EU, where price spillovers are particularly significant. The firm may accept delay rather than agree to a relatively low price and, in the limit, may forgo launch entirely if the government does not accept its minimum ask price.

This trade-off between price and delay is expected to differ across markets and across products within markets. In particular, the larger the potential market for the new drug, the higher the manufacturer's opportunity cost of foregone sales due to launch delay. Thus other things equal, launch is expected to occur sooner in large markets and large market size is expected to (partially) mitigate the positive association between price and speed to market.

More formally, the observed outcomes of price and launch lag reflect a bargaining process between the government and the firm. Bargaining resolves in launch of the product if the government's maximum offer price, P_o exceeds the firm's minimum ask price, P_a . The greater the difference between the government's offer and the firm's minimum ask, $P_a - P_o$, the longer the delay in launch.

This theoretical framework suggests a four-equation structural model. The first two equations model the determinants of the firm's minimum ask price and the regulator's maximum offer. The third equation models the delay in launch, as a function of the firm's ask price and the regulator's maximum offer. The fourth equation models the actual launch price, conditional on launch. Given the limitations of our data, in this paper we estimate a reduced form equation for the delay in launch, as a function of the determinants of the firm's ask price and the regulator's offer price. As a proxy for the government's offer

price, we use the quantity-weighted average price of competitor products in the same therapeutic class as the drug to be launched, in Quarter 3 and Quarter 4 prior to the date of the drug's first launch in any country. This can also be interpreted as the firm's expected price and as a rough measure of the extent of price regulation. The firm's ask price is expected to be higher, the greater the potential for spillovers from that country. In particular, countries in the EU are most exposed to spillovers than non-EU countries, because the EU permits parallel trade between EU member countries, but not from outside the EU. Moreover, several EU countries and Canada use external referencing formally or informally in their price regulatory process. The risk of parallel trade is also expected to be higher for high-volume products than for smaller volume products, for which it is less worthwhile for the parallel trades to incur the fixed costs of obtaining a license etc. However, the larger the potential market, the greater the opportunity cost of delay for the firm. Thus the net effect of market size on the firm's ask price is negative, if the opportunity cost effect dominates the risk of parallel trade effect.

We estimate a reduced-form equation for delay in launch, using expected price and expected sales volume as explanatory variables. We also include an indicator variable for whether the firm is launching in its country of domicile (HOME). This is expected to be positively associated with launch if either regulators tend to favor their domestic firms or simply if firms are more familiar with the regulatory process in their home country or anticipate more favorable market uptake because of being a local firm. We also include 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, hence gains from experience. Since this variable is the same across all countries for a given firm and NCE, it captures the firm's internal experience with the launch process in general, not familiarity with a specific country's regulatory system. This delay in launch equation is estimated using a hazard function, taking into account right censoring, i.e., 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 authorization and application for and approval of price/reimbursement, we can not 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 that is related specifically to disagreement over the price. To some extent, these dates may be endogenous and subject to the decisions and interactions between the manufacturer and the government regulator. For example, in submission of market authorization applications, 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 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. Previous studies indicate that launch is sometimes earlier in the hospital sector. Since regulation in many countries focuses on the retail prices, and delay in obtaining reimbursement approval is most critical for retail sales (which typically account for roughly 80 percent of sales for most products), we focus on the launch of new drugs in the outpatient or retail sector.

Specifically, this study aims to test the following hypotheses with respect to regulated markets:

1. The lower the expected price, the longer the launch delay, controlling for product, firm, and country-specific factors. 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.
3. Within the EU, the common parallel export countries experience longer launch delays, after controlling for expected price and expected sales volume and for the new drugs approved through the EMEA centralized procedure. This would confirm that manufacturers are willing to hold off launch in order to reduce the risk of parallel trade and external reference pricing.

Two firm-specific factors may affect launch delay:

4. *Ceteris paribus*, a firm with more launch experience is predicted to have shorter launch delays.
5. A firm is expected to launch earlier in its home (or headquarter) country, assuming that domestic firms have greater familiarity with the regulatory and political process. On some countries, other factors favoring early launch by domestic firms include potential backlash for a delayed launch and possibly market preference for products of local firms, hence higher opportunity cost of delay, *ceteris paribus*.

Data

Our data are from two databases from IMS Health, a global market research company. IMS Drug Launches, hereafter called DL (<http://www.ims-globla.com/products/lifecycle/launches.htm>) records new drug launches in 60 major markets of the world and records 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 retail markets of the 25 major markets in the 1990s. Table 3 lists the 25 countries. 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 NCEs that were launched in at least one of these markets are potentially global in that there is a strong presumption that they could meet the regulatory standards of other markets. We focus on launch in the outpatient sector because this accounts for roughly 80 percent of total drug sales in most countries and because price regulation focuses on prices for the outpatient sector.³

Using the DL database, we identified a total of 220 NCEs launched between October, 1994 and September, 1999. Of these, we excluded eighty NCEs because they were only launched 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 in our 25 countries between October, 1994 and October, 1998. Of these, 29 NCEs were approved through the EMEA centralized procedure, including 4 biotech products (List A) for which approval through the centralized procedure is mandatory.

For these 85 NCEs, we extracted outpatient launch date (month/year) and other sales characteristics from the IMS MIDAS database (<http://www.ims-global.com/products/sales/midas.htm>). 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 Quarter 3 and Quarter 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. As these 25 study countries include all the major pharmaceutical markets, this first launch date is probably a NCE’s first launch worldwide in the retail market. A NCE’s launch delay in a country, conditional on an observed launch, is simply the difference in months between the global launch date and the country-specific launch date. In the descriptive statistics table (Table 3), we

³ Drug prices for the hospital sector are often negotiated between the hospital and the manufacturer, even in countries that strictly regulate drug prices for outpatient/retail sales.

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 a NCE's therapeutic class. The IMS ATC system, which is similar to the WHO ATC system, classifies drugs by body system (alimentary, cardiovascular, etc), indication, and mechanism of action. There are up to four levels within the ATC system but many therapeutic classes have only three levels. We define a NCE's therapeutic class using its 3-digit ATC. Our 85 global NCEs represent 36 different therapeutic classes. For NCEs that were in a new 3-digit therapeutic class, we used a related 2- or 3-digit therapeutic class for calculating the expected prices and volume.⁴ Data for 5 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 percent of launches did not occur during the study period.

The MIDAS database reports price at the ex-manufacturer level, i.e., a manufacturer's selling price to wholesalers. For each NCE, we defined its 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 launch date. The IMS SU is defined as the smallest dose for each product form, for example, one tablet, one capsule, 5 milliliters 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. However, it should be representative of the expected dosage forms for that country. Moreover, the alternatives have similar or worse problems. Price per pack is biased by 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. We used this expected price rather than the 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, forty five percent of launches and launch prices were not observed during our study period. Note that the MIDAS price data for the US and the UK are upward biased because they are based on list prices and 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 do not reflect all discounts given to pharmacists. However, since these discounts in both countries are usually less in early years of the product life-cycle, omitting these discounts probably does not lead to serious bias for our estimates of

⁴ These therapeutic classes (and their proxies) are C9C (C9), J5C (J5), N7D (N7), and R3J (R3D).

expected launch price. In addition, we include country indicators in some of the statistical models, which should control for any country-specific bias.

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. Moreover, 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 Quarter 3 and Quarter 4 prior to a NCE's first global 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. Again, 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 UK pounds in Quarter 3 and Quarter 4 at the beginning of the study period.

Statistical Model

We used the Cox proportional hazard model to analyze the lag and occurrence of launch. For each NCE, our choice of origin is its first launch date among the 25 countries, with subsequent launches represented by the time lag (in months) between a country-specific launch date and the global launch date. In the Cox model, the hazard of a NCE launch for country i at time t is the product of two factors:

$$h_i(t) = \lambda_o(t) \exp\{\beta_1 x_{i1} + \dots + \beta_k x_{ik}\},$$

i.e., a baseline, unspecified, non-negative hazard function $\lambda_o(t)$ and the exponential of a linear function with k covariates, including expected price, expected sales volume, HOME, SALES, etc. The Cox model is semi-parametric in the sense that it does not specify the baseline hazard function $\lambda_o(t)$ and only estimates the β coefficients using the maximum partial likelihood method. Specifications of $\lambda_o(t)$ lead to parametric proportional hazards models. For example, it becomes the Weibull model when $\lambda_o(t) = t^\alpha$. (Dranove and Meltzer, 1994) The statistical software that we used for the Cox partial likelihood estimation is the PHREG procedure in SAS version 8.01 (Allison, 1995).

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). Except for the Full model (to be defined below), not all variables are present. Log

transformations of expected price, expected volume, and SALES are used as their distributions are skewed and approximately log normal. 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 percent change in the hazard for each one unit change in the explanatory variable.

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, or both. First, the Country Comparison model includes only SALES, main therapeutic class indicators (1-digit ATC indicators), and country indicators. In this model, the country indicators reflect the combined effect of all country characteristics, including expected price, expected market size and other country characteristics, such as the regulatory system. We expected the coefficient for SALES to be positive and those indicators for the lower-price countries, including parallel export EU countries, to be negative. Second, the Expected Price-Volume model includes expected price, expected sales volume, SALES, HOME, and main therapeutic class indicators but excludes country fixed effects. In this model, the coefficients for expected price, expected volume, and HOME are expected to be positive. Finally, we estimated the Full model with all explanatory variables. 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 sales volume, such as bureaucratic delays or country-specific propensities to be a base for parallel exports or for external referencing, beyond the pure price effect.

As described earlier, since 1995 the EU has offered a choice of two alternative routes for market authorization – centralized procedure or mutual recognition.⁵ Initially, the centralized procedure was 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 all countries that require 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.

⁵ Using individual national systems is a third possibility but is unlikely to be a desirable alternative for potentially global NCEs.

Anecdotally, it is hypothesized that the centralized procedure would increase exposure to parallel trade, because authorization occurs in all EU countries with a common dosage form, pack size, labeling etc. 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 Quarter 3 and Quarter 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 net impact on delay of pricing and 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 50 months. Obviously, the earlier a NCE's first launch date, the longer the observation period. Such right censoring applies to all countries so should not induce bias, 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. 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. In this NCE Fixed Effect Cox model, we tested 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 is highest in J (systemic anti-infectives) and lowest in R (respiratory system); the unweighted average expected market size is highest in C (cardiovascular system) and lowest in L (oncology).

Table 2 lists the distribution of the total number of NCEs launched per firm during the study period. A total of 40 pharmaceutical or biotechnology firms were involved in the launch of 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 a jointly venture of two firms first launched a NCE, both firms were identified as the originators. Half of the firms (n=20) only launched 1 NCE during the study period, and the highest number of NCEs launched by one firm is 7. The average SALES for the 40 drug firms is 609 million UK pounds, with a standard deviation of 545 million UK pounds.

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). Countries with fewer launches also tend to have a longer average launch delay for those NCEs that are launched (Figure 2), and fewer NCEs launched within 12 months of the global launch date (Figure 3). The US, the UK, and Germany had the 3 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 ranged from 4.2 months for the US to 23.5 months for Japan. US-based firms launched 36 NCEs, followed by the UK (n=12), Switzerland (n=10), and Germany (n=9).

Countries with fewer launches seem to have a lower (unweighted) average expected price, with Japan being the major exception (Figure 4). There are significant cross-country differences in average expected price (for the 85 NCEs), with an over-13-fold difference between Japan (the highest) and Poland (the lowest). This suggests that, although these two countries both have long launch delays and few launches, the contributing factors are different in these two countries. In Japan, market authorization or regulatory delay in approving a price are likely to be more important contributors to delay than the manufacturer's willingness to accept delay because of a low price. By contrast, in Portugal, the low expected price appears to be the dominant factor. The distribution in unweighted average expected volume (for the 85 NCEs) is even more skewed than for average expected price. 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). In addition, the US's rank in expected volume ranges from 1 to 13 (median = 1); Poland's rank ranges from 1 to the 22 (median = 9).

Cox Regressions

Results from the Country Comparison Cox 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 to the UK, Japan had the most negative coefficient (hazard ratio = 0.071), followed by Portugal (hazard ratio = 0.156) and New Zealand (hazard ratio = 0.185). There are significant differences across several therapeutic classes, with cardiovascular system (C) and gynecological, urological system and sex hormones (G) having relatively short delay. Since the cardiovascular system 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. There are only 2 NCEs in the gynecological, urological system and sex hormones, one of which is sildenafil (Viagra), which may have biased the estimated class effect due to the launch of sildenafil (Viagra) without reimbursement in some countries. These ATC effects remain significant after controlling for expected price and volume, which suggests that other differences in the underlying diseases and their drug treatment choices may play a role. SALES is significantly positive, indicating that the launching firm's global experience accelerates the launch process.

The coefficients for the explanatory variables present in both the Expected Price-Volume Cox model and the Full Cox 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, a 10% increase in expected price or expected volume are associated with a 2.7 percent or 1.0 percent increase in launch hazard respectively. 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 fact that countries with larger expected volume have higher opportunity cost of delay, but also may pose a larger threat of parallel trade, since there is a larger supply pool to divert to parallel exports. In addition, 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 are valuable in reducing launch delay.

With the introduction of country indicators in the Full model, the coefficients for expected price and expected sales volume are essentially unchanged. The coefficient of home country becomes smaller but remains significantly positive. The two alternative specifications -- the NCE Fixed Effect Cox model (Table 4) and the logit model for launch within 12 months (results available upon request) -- further

validate the findings on expected price, expected volume and HOME reported in Table 4 (results available upon request). Compared with the Country Comparison model, many country indicators remain significantly negative and hazard ratios are often larger in the Full model. Since the Full model controls for expected price and volume, the country indicators presumably reflect either bureaucratic delays or expected cross-market spillover effects such as parallel trade and external reference pricing, over and above the related effects that are associated with low price. Japan continues to have the most negative hazard ratio, followed by Portugal and New Zealand. Within the EU, the 6 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. To test whether delays in these parallel exporting countries increased following the introduction of the EMEA in 1995, which accelerated market authorization, we created an indicator variable for NCEs first launched after October 1996, the middle point 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 approval through launch, the hypothesized increase in delay in the post-authorization period may be offset by more rapid authorization after the EMEA.

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, were approved through the centralized procedure, while only 1 out of the 9 cardiovascular NCEs used the centralized procedure. All 6 HIV/AIDS drugs in the systemic anti-infective class that were launched after 1995 used the EMEA centralized procedure. These products faced strong political pressure for rapid launch in all countries, which may have contributed to the choice of the centralized procedure.

Characteristics of the 14 EU countries for these 29 NCEs were summarized in Table 5. 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. The delays/non-launch can be attributed unambiguously to the price/reimbursement system. Average launch delay ranges from 8.1 months for Germany to 17.4 months for Greece; however average delay is not as strongly correlated with number of launches as in the full sample (Figure 5). Similar to the full sample of 85 NCEs in the 25 study countries (Table 3), countries with fewer launches seem to have fewer launches

within the first 12 months after global launch (Figure 6). Whereas in the full sample the UK ranked third and second, after the US, in number of drugs launched and average launch delay respectively, in the EMEA sample the UK drops to fourth in number of launches and third in mean delay. This pattern of relatively slower launch in the UK in the post-1996 period is consistent with the hypothesis that review by the National Institute of Clinical Excellence (NICE) may have slowed the launch of drugs in the UK, relative to other less regulated markets of Europe. However, such conclusions are tentative because of the small sample size. Among the 14 EU countries, France, Italy, and Portugal have the lowest average expected prices, deviating significantly from the other countries, and there appears to be a positive association between the number of EMEA NCEs launched and the average expected price (Figure 7). 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 by therapeutic classes (see Table 5).

The Cox model analysis for the centralized procedure subgroup 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 model, the effect of expected price is greater for the EMEA subgroup (hazard ratio 1.67) than for the full sample (hazard ratio 1.27). In the Full model, the coefficient and hazard ratio for expected price is similar in the EMEA subgroup and the full sample but its 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. The same list of countries -- Portugal, Italy, Greece, Belgium, Spain, and France -- have significant negative country effects on launch, controlling for expected price and volume (all $p < 0.0001$). Thus these findings in the full model appear to be attributable to the price regulatory systems in these countries, not to their market authorization systems. Among the 29 NCEs, four NCEs (2 in therapeutic class S, 1 in D, and 1 in L) were not launched in any EU countries during the study period. Exclusion of these NCEs did not affect the results. The NCE Fixed Effect Cox model (Table 6) and the logit sensitivity analyses (available upon request) 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 percent used the centralized procedure; for 4 of these 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, controlling for FIRST, and was removed from the logit model. The negative effect of expected EU volume is consistent with the hypothesis that large potential market size, hence high risk of parallel trade, discourages use of the centralized procedure. The similar 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 to 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 of 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 these two outcomes. 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 13 in France during our study period.

In general, the countries that have strict price regulation tend to have fewer products launched and longer delays. This is confirmed by the multivariate Cox proportional hazard model. We find that countries/products with lower expected prices experienced longer launch delays. The magnitude of the expected price effect is similar in the EMEA sample and the full sample. Since all 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 delays in launch that are due to price regulation.

Controlling for expected price, countries with strict regulation and that are likely major parallel exporters (Portugal, Italy, France, Belgium, Spain, and Greece) also have negative country fixed effects that presumably reflect delays due to the bureaucratic process or expected parallel trade effects, beyond the pure price effect. Because the sample is censored after September 1999, it is possible that some NCEs have or will subsequently be launched in the lower-price countries. However, this censoring bias should not affect our estimates of cross-country effects since it applies equally to all countries. 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 the drugs were launched disproportionately by firms from these countries.

Controlling for expected price and country fixed effects, 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. These findings are robust to alternative specifications. Finally, firms with more global launch experience, indicated by the baseline worldwide outpatient sales, have smaller launch delays.

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 return.

We do not attempt to draw policy conclusions from this analysis. Such conclusions would require knowing the effect of delays in launch of new drugs on use of other medical services, on the direct and indirect costs of medical care and on health outcomes. The foregone health benefits from delay in launch are likely to be greater for NCEs that are truly innovative, but there is no consensus measure of this.⁶ Further, our measure of launch in the outpatient sector is only a rough measure of availability of a drug to patients. Some new drugs are launched in the hospital sector before the outpatient sector, so patients may have some access before our observed launch date. Conversely, even after the outpatient launch, availability of a new drug may limit by protocols and, in some cases, by financial barriers if the drug is

⁶ There is no universally accepted indicator of the innovativeness and importance of a new drug. The FDA rating is only available for those drugs that were launched in the US. In any case, it does not necessarily reflect the market's evaluation of the importance of a drug or its expected commercial success (see, for example, Dranove and Meltzer (1994), which is measured by our expected price and expected market size variables.

not covered by insurance or only with significant patient copayment. To the extent that delay reflects real uncertainty as to whether the new drug is cost-effective and worth paying for, 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 primarily rational strategies by manufacturers to avoid price spillovers from low price to high price countries, this would suggest that policies that support parallel trade and external referencing might be imposing significant costs in terms of foregone access to new drugs.

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Table 1. Distribution of 85 NCEs and 25 EMEA-CP-Approved NCEs by 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 85 NCEs by Firm.

| Number of NCEs | Number of Firms |
|----------------|-----------------|
| 1 | 20 |
| 2 | 9 |
| 3 | 4 |
| 4 | 3 |
| 5 | 2 |
| 6 | 1 |
| 7 | 1 |
| Total | 40 |

Table 3. Country Characteristics for 85 Global NCEs.

| COUNTRY | Launched NCEs | Launch Delay (if launched) | | Launched in 12 months | HOME | Expected Price | | Expected Volume | | Expected Price Rank | | | Expected Volume Rank | | |
|---------------|---------------|----------------------------|------|-----------------------|------|----------------|-------|-----------------|--------|---------------------|-----|-----|----------------------|-----|-----|
| | | Mean | STD | | | Mean | STD | Mean | STD | Median | Min | Max | Median | Min | Max |
| AUSTRALIA | 43 | 14.1 | 7.6 | 17 | 0 | 0.377 | 0.418 | 58063 | 70201 | 16 | 2 | 25 | 11 | 4 | 20 |
| AUSTRIA | 54 | 12.4 | 9.4 | 31 | 0 | 0.540 | 0.641 | 22179 | 26904 | 13 | 1 | 22 | 16 | 10 | 25 |
| BELGIUM | 41 | 18.2 | 7.6 | 8 | 0 | 0.525 | 0.541 | 27298 | 27544 | 9 | 1 | 21 | 15 | 9 | 25 |
| CANADA | 56 | 12.2 | 7.8 | 28 | 0 | 0.462 | 0.413 | 73840 | 84062 | 11 | 2 | 24 | 8 | 4 | 18 |
| CZECH | 31 | 21.4 | 9.7 | 6 | 0 | 0.202 | 0.250 | 25748 | 36590 | 23 | 4 | 25 | 18 | 8 | 24 |
| DENMARK | 62 | 11.8 | 8.9 | 39 | 3 | 0.557 | 0.539 | 14603 | 14938 | 9 | 1 | 25 | 18 | 10 | 25 |
| GERMANY | 66 | 8.8 | 8.7 | 50 | 10 | 0.538 | 0.574 | 268216 | 320052 | 11 | 1 | 23 | 3 | 1 | 9 |
| FINLAND | 57 | 11.6 | 8.4 | 37 | 1 | 0.568 | 0.587 | 15158 | 17856 | 10 | 1 | 21 | 20 | 12 | 25 |
| FRANCE | 45 | 14.9 | 9.1 | 19 | 7 | 0.347 | 0.338 | 228560 | 224945 | 15 | 2 | 25 | 3 | 1 | 11 |
| GREECE | 45 | 18.6 | 10.1 | 10 | 0 | 0.421 | 0.427 | 22089 | 27713 | 15 | 2 | 25 | 16 | 10 | 22 |
| HOLLAND | 48 | 10.2 | 8.3 | 34 | 0 | 0.583 | 0.594 | 35733 | 38902 | 8 | 1 | 20 | 13 | 6 | 23 |
| IRELAND | 44 | 10.0 | 8.6 | 30 | 0 | 0.420 | 0.464 | 7165 | 9711 | 15 | 8 | 23 | 24 | 15 | 25 |
| ITALY | 44 | 17.2 | 9.3 | 13 | 1 | 0.345 | 0.293 | 134928 | 167211 | 18 | 1 | 24 | 5 | 2 | 12 |
| JAPAN | 13 | 23.5 | 16.7 | 4 | 4 | 0.969 | 1.157 | 234705 | 378785 | 3 | 1 | 25 | 5 | 1 | 24 |
| MEXICO | 45 | 14.8 | 9.4 | 19 | 0 | 0.248 | 0.263 | 43998 | 57491 | 21 | 3 | 25 | 13 | 2 | 25 |
| NEW ZEALAND | 28 | 13.4 | 6.6 | 11 | 0 | 0.501 | 0.643 | 9730 | 14548 | 14 | 1 | 24 | 22 | 14 | 25 |
| NORWAY | 47 | 15.5 | 8.7 | 17 | 0 | 0.562 | 0.564 | 12217 | 13371 | 10 | 1 | 23 | 21 | 15 | 25 |
| POLAND | 31 | 20.5 | 7.9 | 3 | 0 | 0.075 | 0.065 | 84969 | 120081 | 25 | 5 | 25 | 9 | 1 | 22 |
| PORTUGAL | 26 | 22.1 | 11.0 | 4 | 0 | 0.335 | 0.321 | 32869 | 44744 | 18 | 5 | 24 | 14 | 9 | 24 |
| SOUTH AFRICA | 38 | 14.4 | 6.8 | 12 | 0 | 0.409 | 0.383 | 11639 | 22264 | 12 | 2 | 24 | 23 | 9 | 25 |
| SPAIN | 49 | 15.7 | 8.0 | 16 | 0 | 0.403 | 0.484 | 107530 | 111375 | 18 | 6 | 25 | 7 | 3 | 12 |
| SWEDEN | 62 | 7.8 | 7.1 | 45 | 8 | 0.626 | 0.818 | 35979 | 49392 | 13 | 1 | 25 | 12 | 6 | 25 |
| SWITZITERLAND | 56 | 9.7 | 8.0 | 36 | 14 | 0.681 | 0.677 | 16831 | 19262 | 3 | 1 | 22 | 18 | 5 | 25 |
| USA | 73 | 4.2 | 7.4 | 65 | 38 | 0.681 | 0.488 | 558194 | 596543 | 3 | 1 | 24 | 1 | 1 | 13 |
| UK | 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 | | | | | | |

Table 4. Cox Model Results on the Launch of 85 Global NCEs in 25 Countries.

| Model | Country Comparison Model | | | | Expected Price-Volume Model | | | | Full Model | | | | NCE Fixed Effect Model (Stratified by NCE) | | | |
|-------------------------------|--------------------------|-------|---------|--------------|-----------------------------|-------|---------|--------------|-------------|-------|---------|--------------|--|-------|---------|--------------|
| Variable Name | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio |
| Log (Expected Price) | | | | | 0.236 | 0.035 | <.0001 | 1.266 | 0.220 | 0.047 | <.0001 | 1.246 | | | | |
| Log (Expected Volume) | | | | | 0.094 | 0.020 | <.0001 | 1.098 | 0.141 | 0.035 | <.0001 | 1.152 | 0.236 | 0.042 | <.0001 | 1.267 |
| Log (SALES) | 0.181 | 0.023 | <.0001 | 1.198 | 0.150 | 0.022 | <.0001 | 1.162 | 0.178 | 0.023 | <.0001 | 1.195 | 0.063 | 0.022 | 0.005 | 1.065 |
| HOME | | | | | 1.251 | 0.116 | <.0001 | 3.494 | 0.771 | 0.127 | <.0001 | 2.161 | 1.681 | 0.131 | <.0001 | 5.368 |
| <i>Country Indicators</i> | | | | | | | | | | | | | | | | |
| AUSTRALIA | -1.149 | 0.198 | <.0001 | 0.317 | | | | | -0.887 | 0.203 | <.0001 | 0.412 | | | | |
| AUSTRIA | -0.672 | 0.185 | 0.0003 | 0.511 | | | | | -0.354 | 0.197 | 0.0718 | 0.702 | | | | |
| BELGIUM | -1.278 | 0.201 | <.0001 | 0.279 | | | | | -1.029 | 0.208 | <.0001 | 0.357 | | | | |
| CANADA | -0.675 | 0.184 | 0.0002 | 0.509 | | | | | -0.553 | 0.187 | 0.0031 | 0.575 | | | | |
| CZECH | -1.644 | 0.220 | <.0001 | 0.193 | | | | | -1.093 | 0.242 | <.0001 | 0.335 | | | | |
| DENMARK | -0.380 | 0.179 | 0.0331 | 0.684 | | | | | -0.052 | 0.194 | 0.7869 | 0.949 | | | | |
| GERMANY | -0.094 | 0.176 | 0.5924 | 0.910 | | | | | -0.278 | 0.178 | 0.118 | 0.757 | | | | |
| FINLAND | -0.512 | 0.183 | 0.0051 | 0.599 | | | | | -0.145 | 0.200 | 0.4684 | 0.865 | | | | |
| FRANCE | -1.063 | 0.195 | <.0001 | 0.345 | | | | | -1.077 | 0.197 | <.0001 | 0.341 | | | | |
| GREECE | -1.180 | 0.195 | <.0001 | 0.307 | | | | | -0.842 | 0.207 | <.0001 | 0.431 | | | | |
| HOLLAND | -0.796 | 0.192 | <.0001 | 0.451 | | | | | -0.608 | 0.197 | 0.0021 | 0.544 | | | | |
| IRELAND | -0.924 | 0.196 | <.0001 | 0.397 | | | | | -0.381 | 0.227 | 0.0941 | 0.683 | | | | |
| ITALY | -1.163 | 0.196 | <.0001 | 0.313 | | | | | -1.104 | 0.198 | <.0001 | 0.332 | | | | |
| JAPAN | -2.675 | 0.305 | <.0001 | 0.069 | | | | | -2.801 | 0.308 | <.0001 | 0.061 | | | | |
| MEXICO | -1.077 | 0.195 | <.0001 | 0.341 | | | | | -0.714 | 0.206 | 0.0005 | 0.490 | | | | |
| NEW ZEALAND | -1.694 | 0.228 | <.0001 | 0.184 | | | | | -1.207 | 0.249 | <.0001 | 0.299 | | | | |
| NORWAY | -0.979 | 0.193 | <.0001 | 0.376 | | | | | -0.580 | 0.211 | 0.0059 | 0.560 | | | | |
| POLAND | -1.680 | 0.220 | <.0001 | 0.186 | | | | | -1.174 | 0.237 | <.0001 | 0.309 | | | | |
| PORTUGAL | -1.882 | 0.233 | <.0001 | 0.152 | | | | | -1.539 | 0.241 | <.0001 | 0.215 | | | | |
| SOUTH AFRICA | -1.330 | 0.206 | <.0001 | 0.265 | | | | | -0.852 | 0.229 | 0.0002 | 0.426 | | | | |
| SPAIN | -0.995 | 0.190 | <.0001 | 0.370 | | | | | -0.858 | 0.192 | <.0001 | 0.424 | | | | |
| SWEDEN | -0.163 | 0.179 | 0.3627 | 0.850 | | | | | -0.010 | 0.184 | 0.9551 | 0.990 | | | | |
| SWITZITERLAND | -0.534 | 0.184 | 0.0036 | 0.586 | | | | | -0.379 | 0.194 | 0.0501 | 0.684 | | | | |
| USA | 0.392 | 0.173 | 0.0235 | 1.480 | | | | | -0.138 | 0.191 | 0.4677 | 0.871 | | | | |
| <i>1-digit ATC Indicators</i> | | | | | | | | | | | | | | | | |
| A | -0.303 | 0.130 | 0.0202 | 0.739 | 0.065 | 0.150 | 0.664 | 1.068 | -0.132 | 0.157 | 0.4008 | 0.876 | | | | |
| B | -0.513 | 0.176 | 0.0035 | 0.599 | -0.091 | 0.191 | 0.6356 | 0.913 | -0.191 | 0.202 | 0.3437 | 0.826 | | | | |
| C | 0.425 | 0.116 | 0.0002 | 1.530 | 0.388 | 0.132 | 0.0032 | 1.475 | 0.290 | 0.145 | 0.0459 | 1.337 | | | | |
| D | -0.140 | 0.150 | 0.3518 | 0.870 | 0.213 | 0.155 | 0.1697 | 1.238 | 0.159 | 0.162 | 0.3246 | 1.172 | | | | |
| G | 1.120 | 0.176 | <.0001 | 3.063 | 1.255 | 0.187 | <.0001 | 3.509 | 1.221 | 0.191 | <.0001 | 3.389 | | | | |
| L | -0.053 | 0.121 | 0.6619 | 0.949 | 0.145 | 0.122 | 0.2345 | 1.156 | 0.152 | 0.125 | 0.2245 | 1.164 | | | | |
| M | 0.019 | 0.164 | 0.9065 | 1.019 | 0.208 | 0.165 | 0.2069 | 1.231 | 0.167 | 0.166 | 0.314 | 1.182 | | | | |
| N | 0.218 | 0.100 | 0.029 | 1.243 | 0.481 | 0.123 | <.0001 | 1.617 | 0.355 | 0.129 | 0.0058 | 1.427 | | | | |
| R | 0.181 | 0.145 | 0.2117 | 1.198 | 0.413 | 0.168 | 0.0136 | 1.512 | 0.206 | 0.177 | 0.2451 | 1.228 | | | | |
| S | 0.034 | 0.137 | 0.8031 | 1.035 | 0.223 | 0.140 | 0.1123 | 1.249 | 0.215 | 0.144 | 0.1349 | 1.239 | | | | |
| Chi-Square (DF) | 551 (35) | | <.0001 | | 302 (14) | | <.0001 | | 606 (38) | | <.0001 | | 193 (3) | | <.0001 | |

Table 5. EU Country Characteristics for 29 EMEA-CP-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 | 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-CP-Approved NCEs.

| Model Variable Name | Country Comparison Model | | | | Expected Price-Volume Model | | | | Full Model | | | | Stratified Model (by NCE) | | | |
|-------------------------------|--------------------------|---------|---------|--------------|-----------------------------|---------|---------|--------------|-------------|---------|---------|--------------|---------------------------|-------|---------|--------------|
| | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio | Coefficient | SE | P Value | Hazard Ratio |
| Log (Expected Price) | | | | | 0.512 | 0.161 | 0.002 | 1.668 | 0.253 | 0.170 | 0.138 | 1.288 | 0.421 | 0.200 | 0.036 | 1.524 |
| Log (Expected Volume) | | | | | 0.013 | 0.058 | 0.824 | 1.013 | -0.097 | 0.110 | 0.379 | 0.907 | 0.059 | 0.061 | 0.331 | 1.061 |
| Log (SALES) | 0.069 | 0.038 | 0.072 | 1.072 | 0.069 | 0.039 | 0.079 | 1.072 | 0.090 | 0.040 | 0.024 | 1.095 | | | | |
| HOME | | | | | 0.477 | 0.356 | 0.180 | 1.612 | -0.267 | 0.366 | 0.465 | 0.766 | 0.851 | 0.389 | 0.029 | 2.342 |
| <i>Country Indicators</i> | | | | | | | | | | | | | | | | |
| AUSTRIA | -1.008 | 0.371 | 0.007 | 0.365 | | | | | -1.187 | 0.410 | 0.004 | 0.305 | | | | |
| BELGIUM | -1.208 | 0.350 | 0.001 | 0.299 | | | | | -1.409 | 0.384 | 0.0002 | 0.244 | | | | |
| DENMARK | 0.047 | 0.316 | 0.882 | 1.048 | | | | | -0.178 | 0.384 | 0.643 | 0.837 | | | | |
| GERMANY | 0.341 | 0.318 | 0.284 | 1.407 | | | | | 0.405 | 0.332 | 0.221 | 1.500 | | | | |
| FINLAND | -0.395 | 0.340 | 0.245 | 0.673 | | | | | -0.681 | 0.425 | 0.109 | 0.506 | | | | |
| FRANCE | -1.160 | 0.363 | 0.001 | 0.314 | | | | | -1.031 | 0.370 | 0.005 | 0.356 | | | | |
| GREECE | -1.427 | 0.372 | 0.0001 | 0.240 | | | | | -1.629 | 0.441 | 0.000 | 0.196 | | | | |
| HOLLAND | -0.364 | 0.341 | 0.285 | 0.695 | | | | | -0.512 | 0.362 | 0.157 | 0.599 | | | | |
| IRELAND | -0.819 | 0.362 | 0.024 | 0.441 | | | | | -1.127 | 0.513 | 0.028 | 0.324 | | | | |
| ITALY | -1.855 | 0.424 | <.0001 | 0.156 | | | | | -1.800 | 0.426 | <.0001 | 0.165 | | | | |
| PORTUGAL | -2.366 | 0.506 | <.0001 | 0.094 | | | | | -2.484 | 0.538 | <.0001 | 0.083 | | | | |
| SPAIN | -1.277 | 0.372 | 0.001 | 0.279 | | | | | -1.294 | 0.377 | 0.001 | 0.274 | | | | |
| SWEDEN | 0.213 | 0.312 | 0.496 | 1.237 | | | | | 0.129 | 0.342 | 0.707 | 1.138 | | | | |
| <i>1-digit ATC Indicators</i> | | | | | | | | | | | | | | | | |
| A | 1.384 | 0.267 | <.0001 | 3.991 | 2.539 | 0.490 | <.0001 | 12.667 | 2.386 | 0.503 | <.0001 | 10.874 | | | | |
| B | 0.448 | 0.333 | 0.179 | 1.565 | 1.617 | 0.483 | 0.001 | 5.036 | 1.460 | 0.561 | 0.009 | 4.308 | | | | |
| C | 2.367 | 0.347 | <.0001 | 10.664 | 2.711 | 0.387 | <.0001 | 15.046 | 3.058 | 0.491 | <.0001 | 21.280 | | | | |
| D | -0.676 | 0.384 | 0.079 | 0.509 | -0.150 | 0.390 | 0.700 | 0.860 | -0.556 | 0.427 | 0.194 | 0.574 | | | | |
| G | 2.703 | 0.339 | <.0001 | 14.928 | 3.307 | 0.405 | <.0001 | 27.294 | 3.280 | 0.422 | <.0001 | 26.569 | | | | |
| L | -0.465 | 0.307 | 0.129 | 0.628 | -0.200 | 0.307 | 0.514 | 0.818 | -0.354 | 0.314 | 0.259 | 0.702 | | | | |
| M | 1.626 | 0.342 | <.0001 | 5.085 | 1.512 | 0.340 | <.0001 | 4.538 | 1.691 | 0.347 | <.0001 | 5.425 | | | | |
| N | 1.475 | 0.203 | <.0001 | 4.369 | 2.303 | 0.394 | <.0001 | 10.008 | 2.282 | 0.405 | <.0001 | 9.798 | | | | |
| S | -14.933 | 414.756 | 0.971 | 0.000 | -14.205 | 450.357 | 0.975 | 0.000 | -14.537 | 422.904 | 0.973 | 0.000 | | | | |
| Chi-Square (DF) | 280 (23) | | <.0001 | | 191 (13) | | <.0001 | | 283 (26) | | <.0001 | | 10.4 (3) | | 0.015 | |

Table 7. Logit Model Results on the Choice of EMEA Centralized Procedure.

| Variable | Full Model | | | Reduced Model | | |
|--------------------------|-------------|-------|---------|---------------|-------|---------|
| | Coefficient | SE | P Value | Coefficient | SE | P 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 |

Figure 4.1 Average Access Times for New Molecular Entities first marketed between 1990-1999

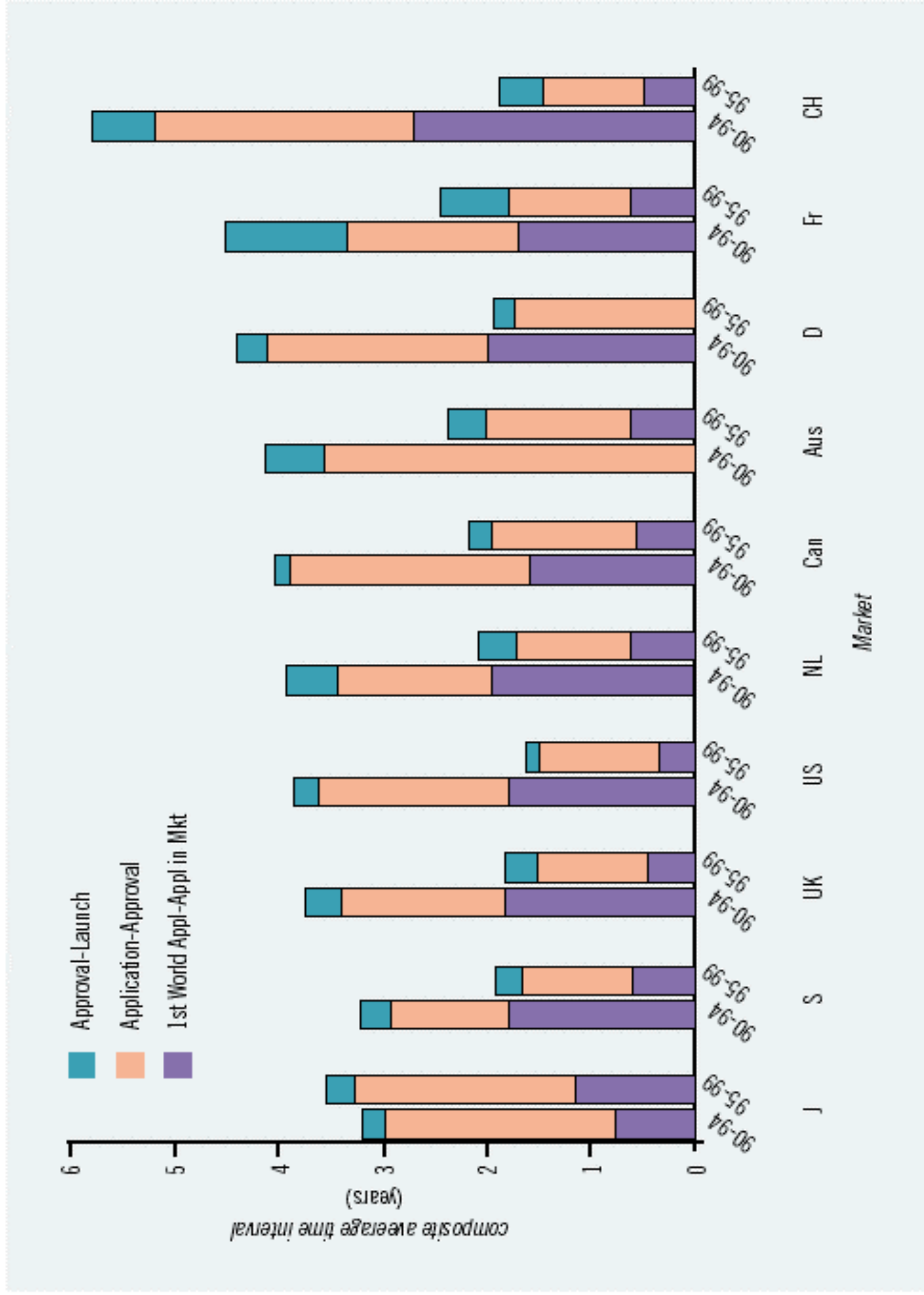


Figure 2. Number of NCEs launched and average launch delay, by country.

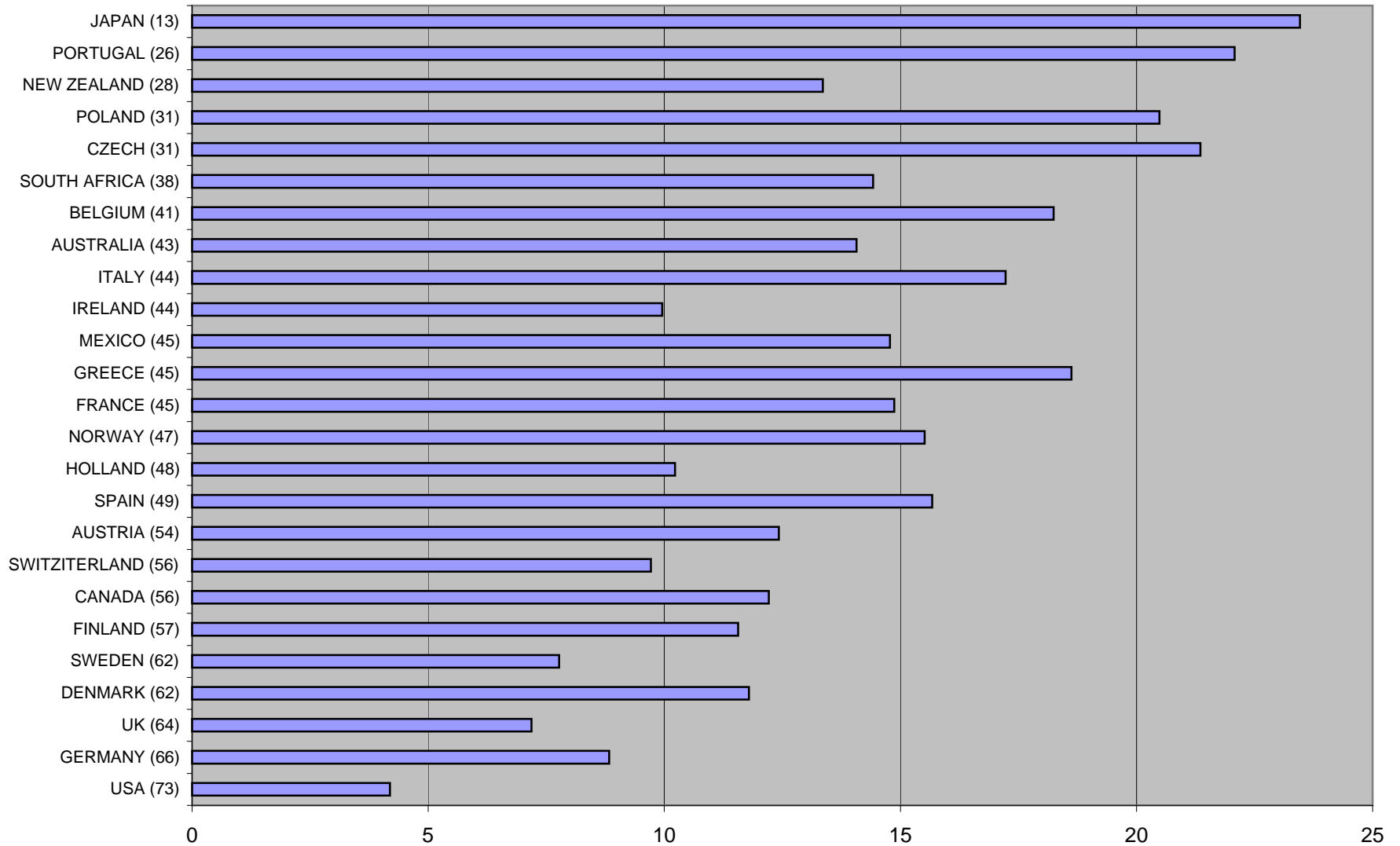


Figure 3. Total number of NCEs launched and number of NCEs launched within 12 months of first global launch, by country.

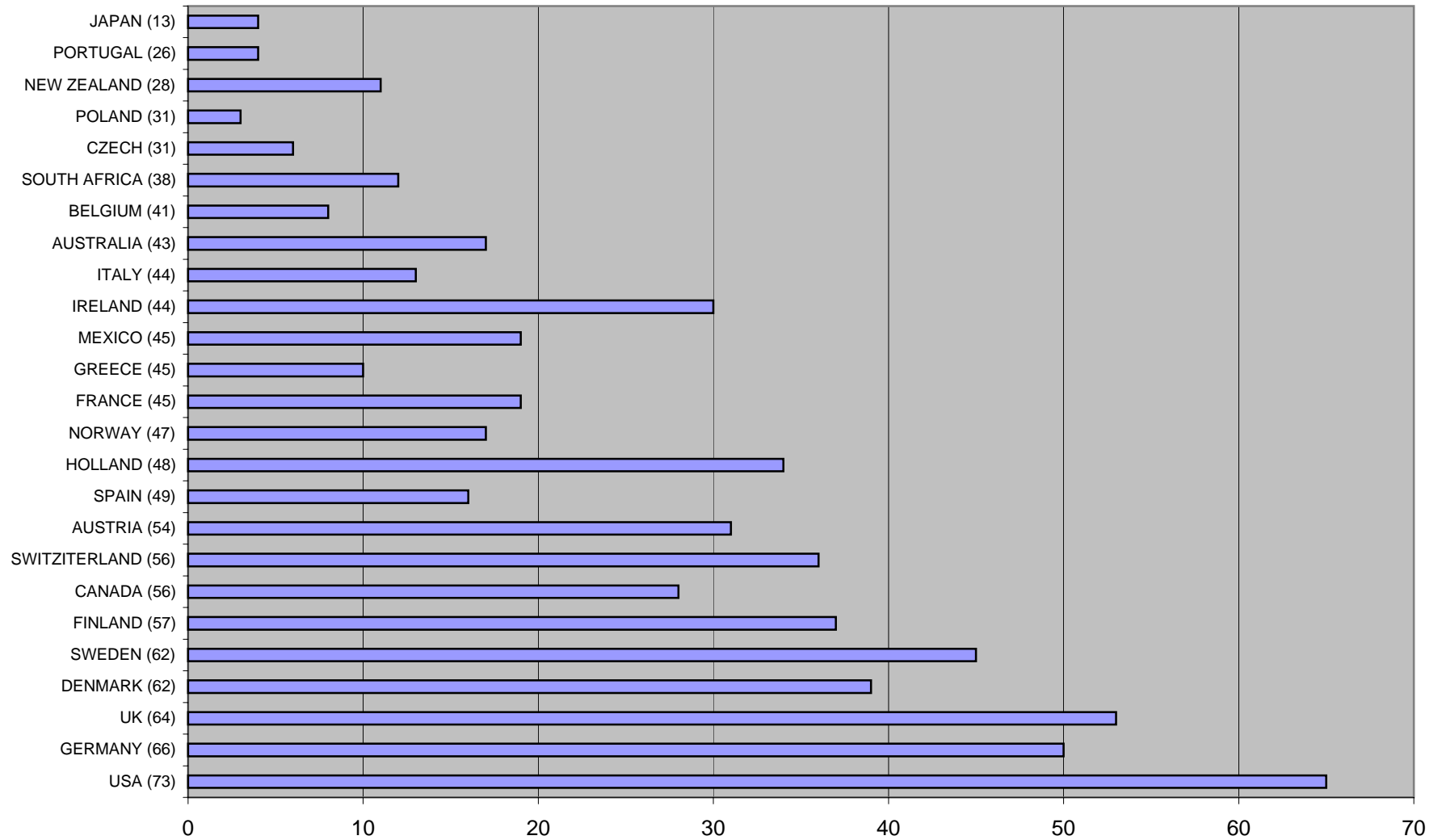


Figure 4. Number of NCEs launched and average expected price, by country.

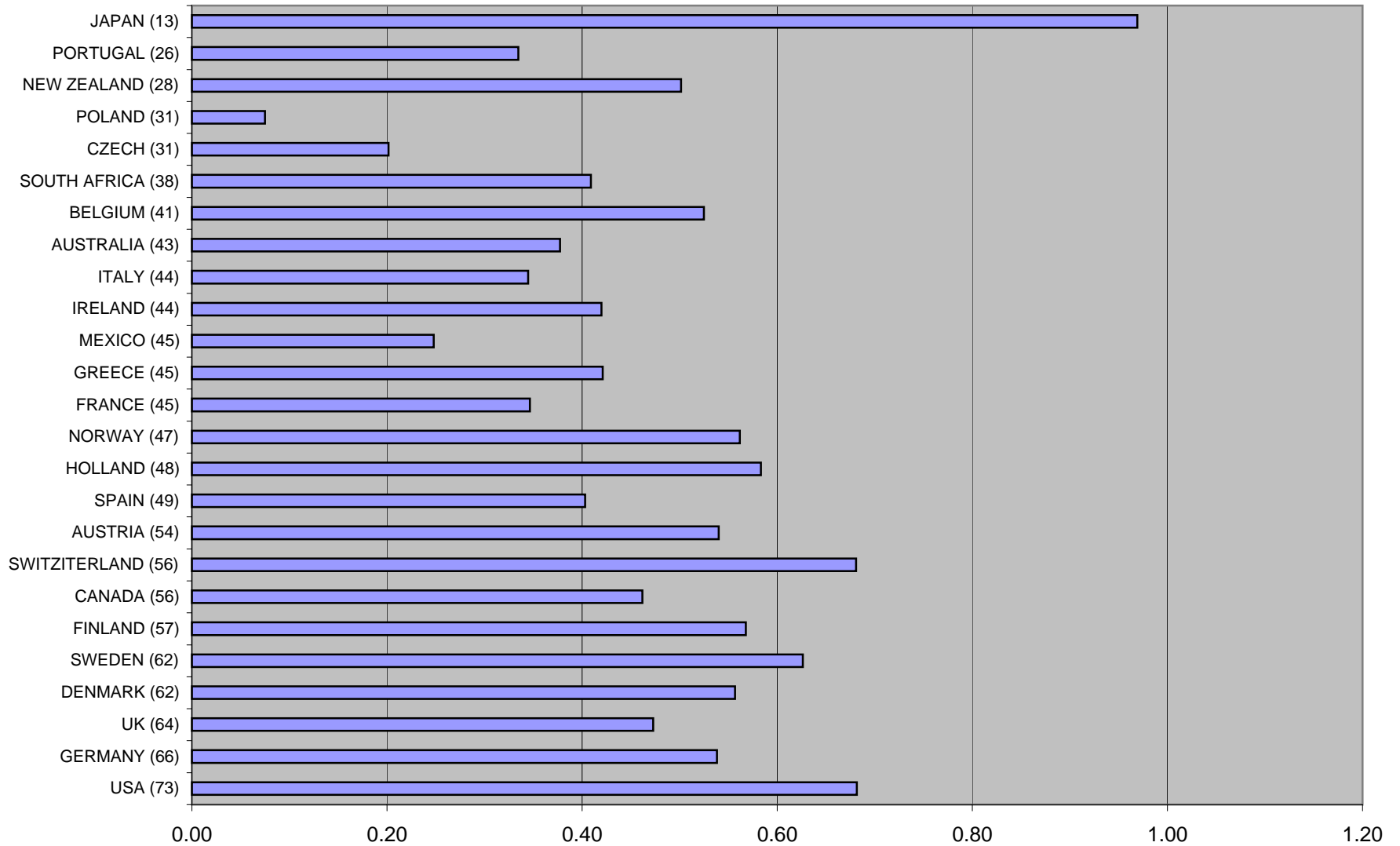


Figure 5. Number of EMEA NCEs launched and average launch delay, EU countries.

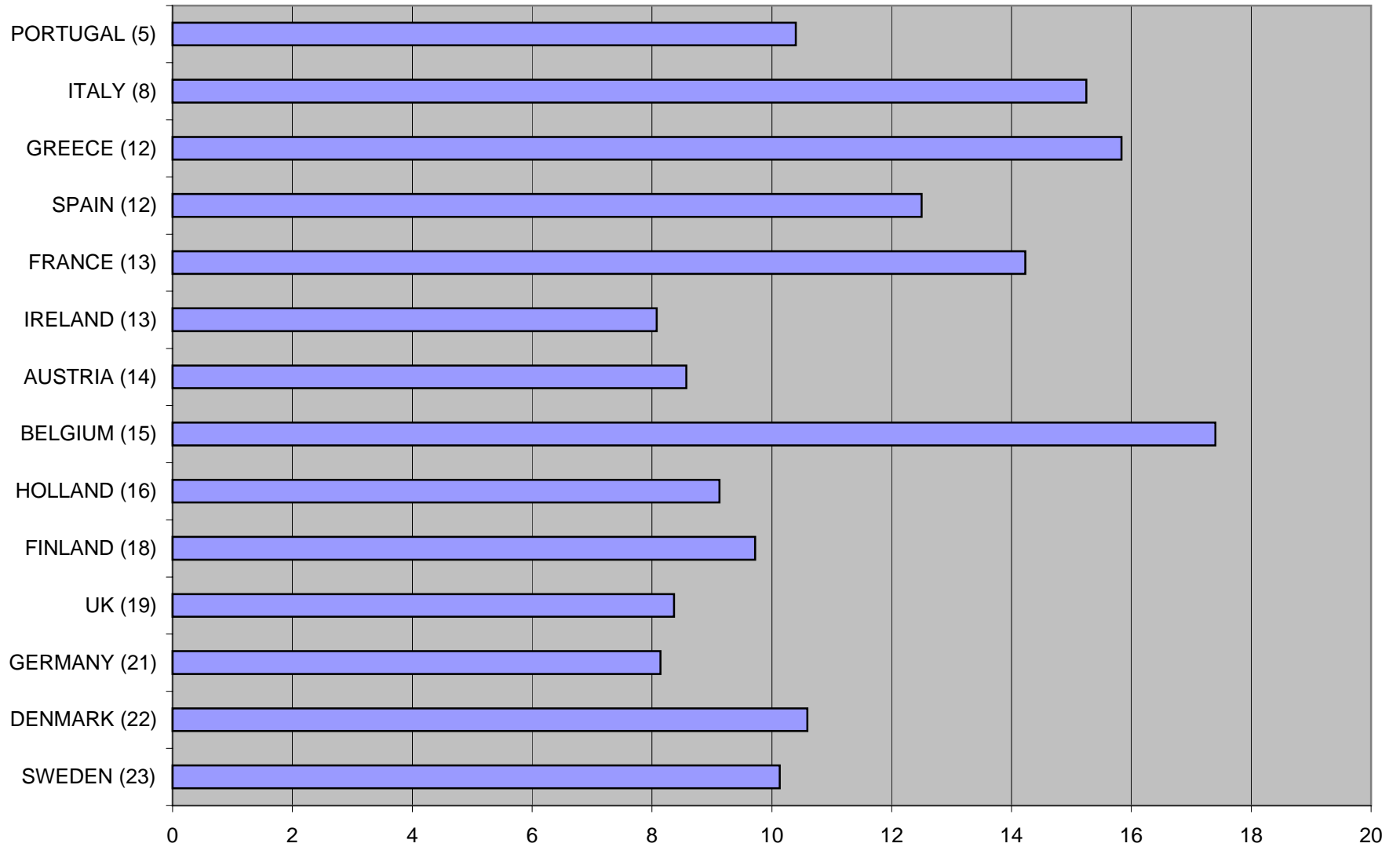


Figure 6. Number of EMEA NCEs launched within 12 months of first global launch, EU countries.

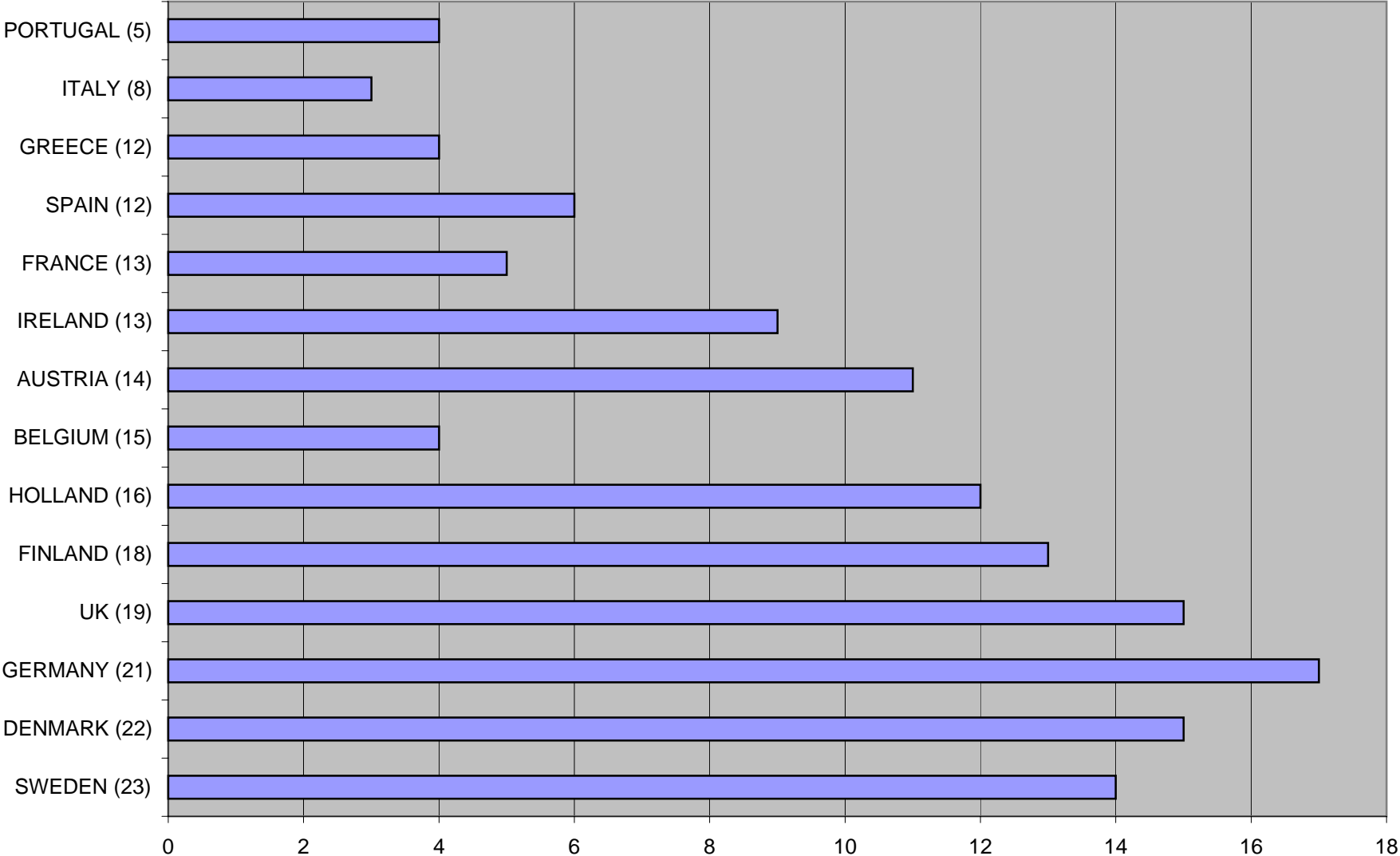


Figure 7. Number of EMEA NCEs launched and average expected price, EU countries.

