Patents and the Global Diffusion of New Drugs

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Analysis of the timing of launches of 642 new drugs in 76 countries during 1983-2002 shows that patent and price regulation regimes strongly affect how quickly new drugs become commercially available in different countries. Price regulation delays launch, while longer and more extensive patent rights accelerate it. Health policy institutions and economic and demographic factors that make markets more profitable also speed up diffusion. The estimated effects are generally robust to controlling for endogeneity of policy regimes with country fixed effects and instrumental variables. The results highlight the important role of policy choices in driving the diffusion of new innovations.
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In 1999 lovastatin, a blockbuster cholesterol drug with annual peak sales of more than $1 billion in the U.S., became commercially available in Egypt—twelve years after it was first approved for sale in the United States. As we will show, this is not exceptional—long launch lags are common and 45 percent of all new drugs are only launched in ten or fewer countries within a decade. Since delayed launch means foregone health benefits, it is important to understand how public policy affects the diffusion of new drug innovations. In this paper we demonstrate that the patent and price regulation policies governments adopt have a powerful impact on the speed at which new drugs become available in different countries.

Promoting affordable access to new drugs is a central objective of government policy. This poses two key challenges: providing adequate incentives for the development of new drugs, and ensuring affordable prices of drugs once developed. Governments use two main instruments to achieve these goals: patents and price regulation. The innovation literature emphasizes a basic tradeoff between the welfare gains from stronger innovation incentives provided by patents and the welfare loss created by the resulting

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higher prices.[1] Reflecting this concern, most research on patents and 'access' to drugs has focused on how the 1994 TRIPS Agreement, which mandated global harmonization of pharmaceutical patent rights, affected prices in emerging markets (Chaudhuri, Goldberg and Gia (2006); Duggan, Garthwaite and Goyal (2014); Kyle and Qian (2014)).[2]

In the debates over TRIPS (and more recently, the proposed Trans-Pacific Partnership trade agreement), developing countries and public health advocacy groups have argued that harmonization of patent policy is both unnecessary and harmful when viewed from the perspective of this tradeoff. For low income countries with limited private health insurance and poorly funded public health systems, the welfare loss involves not just the deadweight loss from higher prices, but also the worrying prospect that large segments of the population may have no affordable access to new drug therapies. This has led economists to recommend alternative ways for governments to provide innovation incentives while maintaining low prices in developing countries, especially for vaccines (Kremer (1998), Kremer (2002)). Moreover, the increase in innovation incentives from having patent rights in low income countries is likely to be small for many kinds of drugs because these countries do not account for a large part of the global market.[3]

This debate, however, misses a critical element: the impact patent rights and other policies have on the *diffusion* of new drugs. The public health benefits of new drugs depend, first, on how quickly (if at all) drugs are launched in different countries and, second, on how widely they are adopted within a country, once launched. Once a drug has been developed, sunk R&D costs are not relevant to the launch decision. However, the decision to launch in any given country will be sensitive to drug manufacturers' assessment of anticipated profits relative to country-specific costs. These include costs of clinical trials to secure regulatory approval and commercial costs relating to product launch, such as establishing distribution capacity, educating prescribers, and obtaining reimbursement from private or public insurers. These costs must be incurred in every country in which a drug is launched: outside tightly integrated trading blocs such as the European Union, there are few international protocols that recognize regulatory approval of drugs across borders, and limited economies of geographic scope in distribution. Moreover, it is likely that the bulk of these entry costs would apply whether the first entrant in a country is the original innovator, its licensee or a generic imitator.

Of course, if these costs were negligible, diffusion would be driven exclusively by heterogeneity in demand side factors affecting the benefits of adoption in different coun-

[1]The classic statement is Arrow (1962), which spawned a huge literature. Empirical studies of the impact of patent rights on the rate and direction of innovation are more recent, and include Sakakibara and Branstetter (2001), Moser (2005), Qian (2007), Kyle and McGahan (2012), Williams (2013), Galasso and Schankerman (2015), and Budish, Roin and Williams (2013).

[2]TRIPS is the acronym for the Agreement on Trade-Related Aspects of Intellectual Property Rights, which is administered by the World Trade Organization. Sell (2003) discusses the political economy of TRIPS and other international trade-related agreements. Grossman and Lai (2004) provide a theoretical analysis of patent regimes in a trading world economy with different market sizes and capacity for innovation.

[3]An important exception to this are drugs for 'neglected diseases' whose burden falls disproportionately on the population of low-income countries. With little or no market for these drugs in high-income countries, the strength of intellectual property rights in emerging markets could play a larger role in innovation incentives (Lanjouw and Cockburn (2001)). However, patents are not the only way to provide incentives to do R&D in these areas, e.g. Ridley, Grabowksi and Moe (2006) who proposed the transferable Priority Review Voucher mechanism now implemented in the USA.

tries. This is the perspective emphasized in the economics literature on diffusion, beginning with the seminal work by Griliches (1957). But if the sunk investments required to enter and penetrate new markets are significant, the diffusion of new technologies will also be influenced by policies that affect profitability of suppliers in different markets, including patent rights. This supply-side perspective is at the heart of economic models of entry (e.g., Bresnahan and Reiss (1987); Holmes (2011); Collard-Wexler (2013)), and has been underappreciated as a factor limiting diffusion of innovations across different markets. Of course, the potential role of patent rights in promoting global diffusion of innovation is not limited to pharmaceuticals, but they are a good case study both because of their economic importance and the significant country-specific costs of launching new drugs.

In this paper we focus on how patent and price control policies, as well as economic and demographic factors, affect the speed and scope of diffusion of new pharmaceutical products across countries.[4] The empirical analysis is based on a large data set that covers launches of 642 new drugs in up to 76 countries during the period 1983-2002, together with information on the patent and price control regimes in these countries. More than in previous research, the countries in our data set span all levels of economic development and exhibit a wide variety of patent regimes. In the analysis we distinguish between process patents, which protect of methods of manufacture, and product patents on new chemical molecules. Process patents are considered relatively weak, as they do not prevent competitive entry by entrants with superior manufacturing processes. Some countries (such as India) purposefully adopted a 'process only' patent regime for drugs in order to foster domestic competitive entry. Product patents are typically considered stronger rights, blocking entry by competitive (or generic) products and allowing for more effective appropriation of rents. The wide variation across countries, and over time within countries, in both the duration and content of patent regimes provides the potential to identify effects of policy choices on diffusion.

There are four main empirical findings. First, we document the limited scope and slow pace of global diffusion of new drugs. Many new drugs become available in countries only after long lags (often more than 10 years) from the date at which they were first launched commercially, and many drugs are never launched outside a handful of wealthier countries. Second, we show that the patent policies governments adopt strongly affect how quickly new drug therapies are launched in their countries. Longer, and stronger, patent protection powerfully accelerates diffusion. For example, controlling for economic and demographic factors, moving from a regime of no product patents to a long product patent term reduces launch lags by about 55 percent. The magnitudes of these effects are even larger when we account for the endogeneity of patent and price control regimes, using country fixed effects and instrumental variables. Process patents also pro-

[4] A launch decision in one country may also depend on policy regimes in other countries. Such 'policy externalities' can arise from benchmark pricing formulas (Bloom and Van Reenen (1998); Jacobzone (2000); Brekke, Grasdal and Holms (2009); Kyle (2007)), and parallel trade that erodes price differences across country borders (Ganslandt and Maskus (2004)). In this paper we focus on how domestic policies affect launch lags, but do not incorporate these policy externalities. A full treatment of dynamic entry decisions across markets with spillover effects remains an important topic for future research.

mote faster launch, but the impact is not as large as for product patents. Short product patents have no effect. Importantly, we show that the impact of policy regimes holds equally for low and middle income countries as for high income countries.

Third, countries that adopt strong pharmaceutical price controls experience significantly longer launch lags for new drugs. We estimate that introducing price controls increases launch lags by about 25 percent, and with instrumental variables the estimate rises to more than 80 percent. Fourth, new drugs are launched much faster in countries that have health policy institutions that promote availability and distribution of drugs—in particular, adopting the Essential Drug List of the World Health Organization and having a National Formulary—and these institutions do not appear to be simply proxies for unobserved institutional quality.

Finally, we find that local market size—as captured by population, per capita income, health expenditures, and demographic factors—has a big impact on the speed of drug launches. These results are consistent with earlier important studies of drug diffusion focused primarily on OECD countries (Kyle (2006), Kyle (2007)), and related research using U.S. data showing that market size is associated with greater pharmaceutical innovation and nongeneric entry (Scott Morton (1999); Acemoglu and Linn (2004); de Mouzon et al. (2011)).

Previous research on patent rights and diffusion of technology has focused on two channels, international trade and foreign direct investment. Delgado, Kyle and McGahan (2013) show that the timing of implementation of TRIPS (compliance dates varied across countries) is associated with increased trade flows in sectors that are IP-intensive relative to a control group. The impact varies substantially across sectors, and notably lower in biopharmaceuticals (compared to ICT), where complementary resources in distribution play a large role. Branstetter, Fisman and Foley (2006) use firm-level data to show that royalty payments and R&D investment by multinational affiliates increase after IP reforms were adopted in sixteen countries (some before TRIPS), and that this effect is concentrated among affiliates of parent companies that use U.S. patents extensively prior to the reforms. In both of these papers, the patent reforms are treated as exogenous events.

The first important empirical research on international *drug diffusion* is Kyle (2006) and Kyle (2007).[5] The 2007 paper uses launch data in 28 countries (21 of which are OECD members) from 1980-2000 and shows that price controls significantly retard the speed of launch as well as the number of countries in which a drug is launched. Interestingly, firms are also found to less likely to follow launch in a low-price country with launch in a high-price country, possibly due to 'reference pricing' policies by pharmaceutical price regulators. In her work, the price control regime is treated as exogenous and, due to limited time variation, country fixed effects are not used. Moreover, her paper does not examine the impact of patent rights on drug launch dates, and has much less coverage of low and middle income countries as compared to the sample we use here. This latter point is important because critics often claim, without corroborating evidence, that patent rights are unlikely to be as important in emerging and poor countries.

[5] See also Danzon, Wang and Wang (2005).

Kyle (2006) analyzes a similar sample of drug launches in a smaller set of developed G7 countries, focusing primarily on how *firm* characteristics affect launch timing, possibly because they are correlated with unobserved entry costs. [6] Both of these studies also incorporate various controls for market size and demographic characteristics, and a first attempt to control for competition by existing drugs in the market.

Two more recent important studies focus on how patent rights affect the prices and quantities sold of new drug products. Duggan, Garthwaite and Goyal (2014) study drug sales in India and exploit variation in the (assumed exogenous) timing of patent decisions allowed by the Indian patent system to identify the impact of patent rights. They find a modest average increase in prices of 3-6 percent, and little impact on quantities sold and thus on profitability. They suggest that the impacts may be small because of the ability of the Indian government to institute direct price controls, but they do not explicitly analyze the effects of price regulation or the timing of launch decisions. In related work, Kyle and Qian (2014) provide evidence on the effect of patents on prices and quantities of new drugs, conditional on launch in 59 countries at varying levels of economic development. Kyle and Qian identify the causal impact of patents by comparing drugs which were 'treated' by the implementation of the TRIPS Agreement in a given country with those that were not affected (the difference arises from variations in the date at which a country becomes TRIPS compliant relative to the priority date of the patented drug). Building on the research in the current paper, they also include a selection equation for drug launch. They find that patented drugs have modestly higher prices, though the price premium is smaller in poorer countries, possibly reflecting price discrimination strategies adopted by drug manufacturing firms. Interestingly, they also find that patents are associated with *higher* quantities sold, possibly because patents give firms incentives to increase investment to promote within-country diffusion, as discussed above.

The paper is organized as follows. Section I develops a simple dynamic model of drug launches, as a framework for interpreting our empirical results. Section II describes the data set (details are provided in the Online Appendix). Section III presents nonparametric evidence on the geographic scope and speed of new drug diffusion, and how it varies with patent and price regulation regimes and the level of economic development. Section IV describes the specification of the hazard model for drug launches and presents the main econometric results, followed by robustness checks in Section V. In Section VI we show that the key results are robust to using country fixed effects and instrumental variables to address the endogeneity of policy regimes. Section VII uses our parameter estimates to simulate the impact of counterfactual policy regimes on drug diffusion. We conclude with a short summary of key findings and directions for future research.

[6] It is not possible to make direct comparisons of the samples of molecules studied in the two Kyle papers with our data because of different procedures for constructing the data sets. Overall, we are more conservative in counting drug launches. For more discussion, see the Online Appendix.

I. A Model of Drug Launch

Consider a firm that has developed a new drug i that can be launched in a set of countries, denoted by $j = 1, ..., J$. The firm obtains a product patent on the drug in each country at time $t = 0$.[7] Patent protection lasts for T_j periods in country j, after which generic competition drives price to marginal cost. A launch in country j involves a sunk cost, σ_{ij}.[8] During patent protection, the firm earns flow profit in period t equal to $\pi(x_{ij})\omega_{ijt}$, where ω_{ijt} is a profitability shock and x_{ij} includes observable variables driving flow profits. As detailed below, in our empirical implementation these include market size, demographic characteristics, and policy variables and institutions including the duration and strength of patent rights, and price regulation. For simplicity, here x_{ij} is treated as time invariant. In the empirics we allow x_{ij} to change over time.

We assume ω_{ijt} evolves as an $AR(1)$ process

$$\omega_{ijt} = \lambda\omega_{ij,t-1} + \eta_i + \mu_j + \upsilon_{ijt} \tag{1}$$

where $\lambda \in (0, 1)$, η_i and μ_j are drug and country-specific random effects known by the firm, and v_{ijt} is an iid disturbance.[9] The specification implies that $\Pr(\omega_{ijt} \mid \omega_{ij,t-1})$ is stochastically increasing in $\omega_{ij,t-1}$. The present value of launch at time t, conditional on available information, is

$$E(V_{ijt} \mid \omega_{ijt}, \eta_i, \mu_j) = \sum_{k=0}^{T_j - t} \beta^k \{\pi(x_{ij}) E(\omega_{ij,t+k} \mid \omega_{ijt}, \eta_i, \mu_j)\} - \sigma_{ij}$$

where $\beta \in (0, 1)$ is the discount factor. The firm launches the drug in country j when $E(V_{ijt} \mid \omega_{ijt}, \eta_i, \mu_j) \geq 0$. Given the $AR(1)$ assumption on ω, the optimal entry rule is to launch the drug when the profit shock ω_{ijt} exceeds a threshold level, ω^*_{ijt} (Ericson and Pakes (1995)). This rule applies because $E(V_{ijt} \mid \omega_{ijt}, \eta_i, \mu_j)$ is increasing in ω_{ijt}.

The $AR(1)$ specification for ω implies the following simple closed-form solution for

[7] This assumption simplifies the model. In practice, firms do not always seek or obtain patent protection in all countries. The assumption that the patent clock starts running at the same time in all countries is consistent with international patent treaties which set a global priority date based on first patent application in any country. Note also that drug launches typically occur much later than the patent application date, due to the amount of time needed for subsequent clinical development and obtaining regulatory approval.

[8] The entry cost includes the costs of regulatory approval in the target country (where necessary), investment in distribution channels, providing information to doctors and pharmacies, and securing registration on the national drug formulary for reimbursement. These costs can vary widely across drugs and country of launch.

[9] The random effects allow ω_{ijt} to be correlated across countries for a given drug, and across drugs for a given country, since $E(\omega_{ijt}\omega_{i'jt} \mid \omega_{ij,t-1}, \omega_{i'j,t-1}) = \sigma^2_\mu$ and $E(\omega_{ijt}\omega_{ij't} \mid \omega_{ij,t-1}, \omega_{ij',t-1}) = \sigma^2_\eta$ for $i \neq i'$ and $j \neq j'$.

the entry threshold:[10]

$$\omega^*_{ijt} = \frac{\sigma_{ij} - \Theta(T_j - t)(\eta_i + \mu_j)}{\pi(x_{ij})\frac{1-\phi^{T_j-t+1}}{1-\phi}} \tag{2}$$

where $\phi = \beta\lambda \in (0, 1)$ and $\Theta(T_j - t)$ is an increasing function of remaining patent term, $T_j - t$.

The probability that the drug is launched in country j at time t, given it has not been launched before (the hazard rate of launch), is

$$\begin{aligned} h(t \mid Z_{ijt}) &= \Pr(\omega_{ijt} \geq \omega^*_{ijt} \mid \omega_{ij1} < \omega^*_{ij1}, ..., \omega_{ij,t-1} < \omega^*_{ij,t-1}) \\ &= \Pr(\omega_{ijt} \geq \omega^*_{ijt} \mid \omega_{ij,t-1} < \omega^*_{ij,t-1}) \end{aligned} \tag{3}$$

where $Z_{ijt} \equiv (x_{ij}, T_j, t, \sigma_{ij}, \eta_i, \mu_j)$ is assumed known to the firm, and the second equality follows from the $AR(1)$ assumption on ω. This implies that the hazard rate is a decreasing function of factors that raise the threshold ω^*_{ijt}.

To summarize the predictions: the hazard rate of drug launch in a given country should be increasing in factors that increase flow profit (such as the duration and strength of patent protection, as well as determinants of market size such as population demographics, income, and health expenditures), but decreasing in factors that reduce flow profits, such as price regulation, time elapsed since first launch, and the sunk cost of entry.

II. Data and Measurement

In this section we briefly describe construction of the data set. Details of procedures and sources are provided in the Online Appendix.

A. Identifying drug launches

A launch is defined as the first appearance of the active ingredient of a drug (new chemical entity) in a given country, whether in proprietary or generic form. Determining if, and when, a new drug becomes available in a given country is not straightforward. Since almost all countries require formal approval from a health and safety regulator before a drug can be marketed, administrative records could potentially be used for this purpose. But poor record keeping in some countries, lack of easily accessible public records, and language barriers make it infeasible to track regulatory approvals for large numbers of drugs across many countries, particularly for historical data. Regulatory

[10] From equation (1) and $E(v_{ij,t'} \mid \omega_{ijt}, \eta_i, \mu_j) = 0$ for $t' > t$, we get

$$E(V_{ijt} \mid \omega_{ijt}, \eta_i, \mu_j) = \omega_{ijt}\pi(x_{ij}) \sum_{k=t}^{T_j-t} \phi^k + \Theta(T_j - t)(\eta_i + \mu_j) - \sigma_{ij}$$

where $\phi = \beta\lambda \in (0, 1)$ and $\Theta(T_j - t) = 1 + \sum_{k=1}^{T_j-t} \beta^k \sum_{m=0}^{k-1} \lambda^m$. Setting $E(V_{ijt} \mid \omega_{ijt}, \eta_i, \mu_j) = 0$ yields the entry threshold given in the text.

approvals also do not directly track commercial availability, and formal approval is not the same as de facto launch of a product.

We rely on a compilation of product launches obtained from a commercial market research company, IMS Health Inc. This dataset tracks product launches in all therapeutic classes in up to 76 different countries during the period 1983-2002. Product launches were identified by IMS from a variety of sources, including regulatory approvals, announcements by manufacturers, local media reports, and IMS' active surveillance of distribution channels as part of other data gathering efforts. Because India was not covered by IMS during this period, we supplement this data source with information from an Indian market research company, ORG/MARG, that tracked product launches in a subset of therapeutic classes over the same period.

To track launches accurately, drugs must be unambiguously identified across countries. This is not straightforward. Drugs are not always identified by a nonproprietary name, and the generic names of chemical entities vary over time and across countries, and are not always spelled consistently.[11] Failing to recognize equivalent chemical entities in the data would result in over-counting of new products, undercounting of the number of countries in which a given drug is launched, and inaccurate dating of launches. As detailed in the Online Appendix, it took considerable effort to identify drugs consistently in these data. The source dataset has more than 180,000 observations on product/country launches. These products contained one or more of approximately 9,600 distinct active drug ingredients in use around the world during the sample period, for which we compiled more than 250,000 synonyms from a variety of reference sources. Of these 9,600 distinct active ingredients, most of which entered medical use prior to 1983, we focus on 642 clearly identifiable novel chemical entities that were first introduced anywhere in the world between 1983 and 2002, and then identify the date when they first appear in any product launched in each country. Importantly, to minimize over counting of drugs and thus undercounting of launches per drug, we used a relatively broad criterion to define equivalent products (for example, grouping together all salts and esters of a given 'active moiety').[12]

B. Patent and price control regimes

For each country in our sample, we characterize the domestic patent regime along four dimensions: duration of patent term, coverage of pharmaceutical products, coverage of chemical manufacturing processes, and an index of the strength of patent protection that reflects the degree to which patent law provisions favor patent holders versus potential infringers (*Propatent Index*, which varies from zero to one). These variables are constructed using data from Ginarte and Park (1997), Park (2008), and other reference sources cited in the Online Appendix. Since the mid-2000s patent regimes around

[11] For example, the drug known as acetominophen in North America is known as paracetamol in most other countries, and is sold under more than 50 different brand names around the world.

[12] This procedure may ignore clinically important differences among variants of a drug that would lead a pharmacologist to distinguish them as different products, but it makes our results conservative in the sense that it will tend over-estimate the number of countries in which a new drug is launched. A narrower definition of equivalent products would generate a higher number of new drugs, with launches observed in fewer countries per drug.

the world have converged on the 'TRIPS standard' (e.g., 20 year term, no exceptions for pharmaceutical products), but there was considerable variation between and within countries during the 1980s and 1990s.

We have no reason to believe that the relationship between patent term and hazard of drug launch is linear. Rather than impose a functional form, we use three mutually exclusive dummy variables to capture patent term duration: *Short* = 0 $<$ duration $\leq$ 12 years (from application date); *Medium* = 13 $\leq$ duration $\leq$ 17 and *Long* = duration $\geq$ 18 (the reference category is no patent protection).[13] Since the average period between patent application and marketing approval is about 10 years (Grabowski and Kyle (2007)), a *Short* patent conveys essentially no effective coverage to the patentee. We use two separate sets of these dummy variables, one for product patents and one for process patents. In terms of country/year observations, short, medium and long process patents account for 10.8, 22.3 and 60.0 percent of the sample; for product patents the figures are 6.4, 16.5 and 58.2 percent, respectively. We experimented with different definitions of the cutoffs for these patent duration categories (*Short* 0-10, 0-11 and 0-13; *Medium* 11-16, 12-16, 13-16, 13-17 and 14-16; and *Long* $\geq$ 17, $\geq$ 18 and $\geq$ 19) but the econometric results were generally robust to these alternatives.

Countries implement price controls for pharmaceuticals using a wide variety of often complex schemes (Jacobzone (2000), Kyle (2007)). We focus on systems of explicit price regulation and summarize the variation across countries by coding systems as constituting 'no,' 'some,' or 'extensive' price controls. A price control regime is labeled as 'extensive' if most or all drugs are regulated, rather than just a subset of the market, or if a country's price regulation is identified by commentators as being particularly rigorous. In the sample, 22 percent of country/year observations are coded as having no price controls, 31 percent with some price regulation and 47 percent with extensive controls.[14]

C. Pharmaceutical policy institutions

The observed timing of market entry reflects both the decisions of firms and the efficiency of a country's regulatory process. We capture government policies that promote access to pharmaceuticals by coding three dummy variables for each country-year. The first is whether a country had adopted a national formulary, where listed drugs would be eligible for distribution through a publicly funded health system, typically more widely prescribed, and with payment mechanisms in place. The second is whether a country had adopted the Essential Drug List (EDL) promulgated by the World Health Organization, which indicates that a country's health institutions are oriented towards promoting access to basic drugs. The third is whether a country has a formal 'national drug policy,' i.e. an effort to coordinate industrial policy and domestic regulation to promote access to safe

[13] Where the patent term runs from date of grant rather than date of application, as was the case in the U.S. prior to 1995, we added two years to make the term roughly equivalent to one running from date of application. Results were not sensitive to changing this assumption about the pendency period to three years.

[14] Price regulation regimes were coded from a variety of reports and legal texts, see the Online Appendix. Table A.2 provides information for each country in the sample on the number of years of coverage, number of drugs launched, average percentage of drugs launched within 5 years of their initial launch date anywhere, and the product patent, process patent, and price regulation regimes and their changes over time.

and effective pharmaceuticals. At the start of our sample period, 65 percent of countries had a national formulary, 41 percent had adopted the EDL and 63 percent had issued a national drug policy; by 1997 all countries had adopted all three.

D. Demographic and income variables

We use a set of income and demographic variables to control for variation in the potential demand for pharmaceuticals. These include: population size and the fraction of population over 65 years old, real GDP per capita in purchasing power parity terms, income inequality measured by the Gini coefficient, and health care expenditures as a percent of GDP. We also include measures of the quality of regulatory bureaucracy and the rule of law, both taken from the World Bank.

Many of the explanatory variables are available annually, but others are available only periodically, in which case we use last-observation-carried-forward to infer missing values. The Online Appendix provides details and summary statistics, and a comparison of our data construction with the approach taken by previous studies (notably, Kyle (2006), Kyle (2007)).

III. Drug Diffusion: Nonparametric Evidence

We begin with some nonparametric evidence on the extent and speed of global drug diffusion. Table 1 presents information on the geographic span of drug launches, showing the distribution of the number of countries for which a launch was observed. Recognizing that this tabulation does not account for right-censoring (some drugs may have launched in some countries after the sample period ends), these statistics illustrate a dominant, and striking, feature of these data: diffusion of new drugs around the world is remarkably slow and limited. In the entire sample of new drugs, 39 percent were launched in ten or fewer countries during the sample period, and only 41 percent were launched in more than 25 countries. The mean number of countries experiencing launch is 22.4 (median of 18) out of a possible 76. Even among the wealthier countries with the most developed health care systems, not all drugs became available during the sample period: e.g., only about 60 percent were launched in the U.S., Germany or the U.K. The fact that drugs are not launched more widely can be due to various factors in addition to patent and price regulation policies. In some countries, the size and demographic features of the market, and the presence of substitutes, may limit anticipated demand to a level that does not justify the cost of entry. In addition, demand may be limited by disease incidence, and local regulatory practices may block approval of some drugs.

This limited geographic diffusion suggests a potentially substantial welfare loss. The good news from a welfare perspective is that diffusion is substantially wider for higher quality drugs—identified here as those approved by the U.S. Food and Drug Administration (FDA), which is among the most stringent regulatory agencies in the world (column 3), and the subset of FDA approved drugs that qualified for the priority review process reserved for drugs with potential for significant improvement in treatment or addressing

significant unmet medical need (column 4).[15] For these drugs, more than half are eventually launched in more than 25 countries (though with long lags, as we will see later). But even within this high quality subset, 13 percent of new drugs were launched in no more than three countries within the sample period.

Because launch lags (defined as the time elapsed between first worldwide launch and launch in a given country) can be long and the sample is truncated at 2002, Table 1 likely under represents the true extent of diffusion. To examine the temporal aspects of diffusion, and to address this potential undercounting of launches, Table 2 and Figures 1 through 3 provide nonparametric analyses of time-until-launch that estimate the distribution of launch lags allowing for right-censoring. The figures plot the Kaplan-Meier 'failure' function (i.e., $1 - \hat{S}_t$ where $\hat{S}_t$ is the estimated survival function) while the table reports only the time corresponding to the 25th percentile of launch lags.

Three main findings stand out. First, pooling over all drugs and countries, even after 10 years only 41 percent of drug-country opportunities for a launch were taken up. Even after 20 years or more, less than 50 percent of possible launches had taken place, and as practical matter, many of these drugs may never be launched in large numbers of countries. While not all of the country-years in which a drug was not launched necessarily represent welfare losses (some drugs may have been made obsolete by advances in technology, may have no value in contexts where important complementary technologies or resources for health care are not available, or may only be useful for treating diseases with low incidence in a country), this evidence of limited diffusion is nonetheless disappointing from a welfare perspective. Even in the subsample of FDA approved drugs, only 54 percent were launched in the average country within 10 years. Diffusion of non-FDA approved drugs was much slower and less extensive, with 19 percent of drug-country launch opportunities filled within 10 years.

Second, the pace and extent of diffusion is strongly associated with a country's patent and price regulation regimes. In the second panel of Table 2 and in Figure 1 we show results broken out by a summary measure of each country's patent regime. The duration of patent rights is categorized as None, Short, Medium and Long (recall that we define Short as a patent term of 10 years or less, Medium as 11 to 16 years and Long as 17 years or longer) and a country/year observation is assigned to that category if it had either process and/or product patents in that group. With no patents, the estimated time for 25 percent of drug-country launch opportunities to be filled is eight years, falling to less than 2.6 years with long-duration patents. In the third panel of Table 2 and in Figure 2 we group observations by strong versus no or weak price regulation.[16] In countries with no or weak price regulation, 25 percent of launch opportunities are filled within three years, compared to five years where price regulation is strong. The estimated 'failure' functions plotted in Figures 1 and 2 are very different across categories, and the log-rank test for

[15] Of the 642 drugs in the sample, 66% were approved by the FDA, and 41% of these were priority-reviewed. Dranove and Meltzer (1994) show that FDA screening outcomes are consistent with independent measures of drug quality such as relative sales, citations in the medical literature etc. They also show that approval times are shorter for more important drugs.

[16] In regressions of the type discussed below we found no statistically discernible distinction between weak price controls and no price controls.

homogeneity strongly rejects the null of no difference across categories: $\chi^2(3) = 750$ for patent regimes, and $\chi^2(2) = 267$ for price controls.

Finally, confirming earlier work by Kyle and others, launch delays are strongly related to market size, as proxied by the level of GDP per capita. Measured in terms of the estimated time for 25 percent of possible drug-country launches to take place, the first panel of Table 2 shows that diffusion is strongly related to market size. As shown in the first column, it takes nine years for 25 percent of drugs to be launched in the average low income country, but only two years in high income countries. This income-related disparity persists when we focus only on the higher quality drugs (columns 2 and 3 in Table 2). The full distribution of estimated launch lags broken out by countries' income level is given in Figure 3. (Medium income includes both the lower middle and upper middle income categories of the World Bank.)

IV. Empirical Model and Results

A. Econometric specification

To analyze the timing of drug launches more formally, and control for other covariates, we use a parametric hazard model. A launch is defined as the first appearance of a drug in a given country, whether in proprietary or generic form, and the launch lag is the time elapsed since the first launch of the molecule in any country. We adopt the proportional hazard model with the Weibull distribution, with the hazard of launch for drug i in country j at time t conditional on no launch prior to t given by

$$h(t \mid x_{ij}(t)) = \alpha t^{\alpha-1} e^{x_{ij}(t)'\beta} \tag{4}$$

where t is time elapsed since the drug became "at risk" of launch, $x_{ij}(t)$ is a set of time-varying covariates and the scalar $\alpha > 0$ and vector β are parameters to be estimated. This specification imposes a monotone hazard rate, but it can be either increasing ($\alpha > 1$) or decreasing ($\alpha < 1$) over time. The model in Section I predicts that the hazard rate declines with t : since the remaining patent life falls with t, the threshold profitability shock for launch must be larger to generate rents to cover the entry cost. The parameter estimates of α presented below confirm this prediction.[17] For continuous covariates β_l corresponds to the percentage change in the per period conditional probability of launch due to a unit change in x_l (for discrete covariates, such as patent and price regulation regimes, β_l is the impact in moving from the reference category to the focal regime).[18]

[17] We also experimented with a log-logistic model that is more flexible in that it can generate a distribution with a non-monotonic hazard rate. The parameter estimates from that specification indicated that the hazard declines over time after a few weeks. This is interesting because it suggests that, unlike in most of the literature on the diffusion of innovations, learning about the potential profitability of markets does not appear to be an important factor for the global diffusion of drugs. If this were the case then we should see a hazard rate that increases with time since first worldwide launch.

[18] With time varying covariates, the hazard function at time t is conditional on the entire sequence of covariates up to t, call it $\mathbf{X}_{ij}(t) = \{x_{ij}(s) : s \leq t\}$. Thus the marginal impact of a covariate on the survival probability and hence the launch lag will depend on the sequence $\mathbf{X}_{ij}(t)$. In our later discussion of how covariates affect predicted launch lags, we focus on the coefficients β. In Section VII we use the estimated coefficients to compute the marginal effect of covariates on the launch lag for each drug-country pair, and then average these marginal effects over pairs using their specific sequence $\mathbf{X}_{ij}(t)$.

Equivalently, we can interpret the negative of β (scaled by the estimated α) as the effect of a unit change in covariates on the predicted log time until launch.

For any given drug, the hazard of launch is likely to differ across countries for reasons other than a country's economic and demographic characteristics and policy regime, for example if the incidence of the relevant disease varies across countries. We address this in three ways. First, we include a set of 14 therapeutic class dummies in all regressions. This allows the baseline hazard rate to be different for each group of drugs. Second, in all regressions we use standard errors clustered over the multiple observations on a drug-country combination. Finally, as a robustness check we include random drug effects.

B. Baseline results

Table 3 presents maximum likelihood estimates for various specifications of the hazard model. In column 1 the control variables include elapsed time since first global launch, the set of patent and price control policy dummies, population and per capita income to control for market size, a dummy variable for whether the drug was approved by the FDA (as an indicator of drug quality), and a set of therapeutic class dummies. The estimated Weibull parameter, α, is 0.614, statistically different from one and stable across specifications. This implies a declining hazard of launch, consistent with the theoretical model.

We begin with the key policy variables. The first important result is that extensive price controls significantly delay drug diffusion. Having strong price regulation reduces the hazard of launch by 15 percent, equivalent to a 25 percent increase in the predicted launch lag.[19] This is qualitatively consistent with, though not directly comparable to, the findings of Kyle (2007) who uses a discrete hazard specification, a smaller set of 28 countries, and a different measure of price controls.

Second, we find that both process and product patents strongly affect launch lags. Since the dummies are defined to be mutually exclusive within the process and product patent categories, the estimated coefficient on *Short_Process* implies that, relative to having no patent protection, a short process patent regime—such as that used by India between 1971 and 2005—reduces launch lags by 19 percent.[20] Moving to *Medium_Process* gives an incremental gain of 13 percent. The coefficient on *Long_Process* is smaller (and not statistically significant), suggesting that long duration process patents do not support market entry based on proprietary process innovation. (This is not clear-cut, however, since we show later that the *Long_Process* coefficient is significant when we account for endogeneity of policy regimes).

[19] We also tried using two separate dummy variables for weak and strong price regulation in a variety of specifications not reported here. We consistently found that weak controls have no statistically significant effect on launch lags. Therefore, in all specifications reported in the paper we use only one dummy variable for strong regulation, and combine country/year observations with weak and no controls as the reference group.

[20] The coefficient on *Short_Process* is identified off a relatively small number of observations: only a handful of countries in the sample had this type of patent regime, and some for only limited periods of time, and it is possible that the estimated effect is confounded with unobserved aspects of their internal market. One of these countries was India, which may be a special case in terms of the size of its internal market and success in developing a highly competitive export-oriented generic sector during this period.

Third, we find that long duration product patents have a powerful effect on diffusion. Short and medium product patents do not strongly affect diffusion time relative to no patent protection, which is not surprising given long clinical development and regulatory lags (and the fact that patents are taken out very early in the R&D process to ensure priority). In contrast, long product patents reduce launch lags by 55 percent.[21] The results are robust to different definitions of the patent term for both process and product patents, as discussed in Section II.[22] In addition to length of patent term, the *content of patent protection* also matters for diffusion. The point estimate of the *Propatent Index* is statistically significant and implies that a one standard deviation increase in the index reduces predicted launch lags by about 11.3 percent.

Turning to control variables of interest, we find that larger market size—as measured by population and GDP per capita—is associated with faster diffusion of new drugs. The estimated coefficients on population and GDP per capita are equivalent to elasticities of launch lags of about -0.12 and -0.40, respectively. This finding is consistent with the conclusion of previous studies based on smaller samples of countries, and the incentive effects of larger markets are also found in the studies of pharmaceutical innovation discussed above. Second, the coefficient on the dummy for FDA approved drugs confirms that high quality drugs are launched much faster—their per period hazard is more than double that of low quality drugs, and their predicted time to launch is less than half of the lag for low quality drugs. Finally, there are significant differences in the speed of drug diffusion across therapeutic classes. Coefficients on the therapeutic class dummies (not reported) range from -0.81 to 0.26, equivalent to launch lags over 130 percent faster or almost 60 percent slower than the reference category, and we strongly reject the null hypothesis that there are no therapeutic class differences (p-value < 0.001). This holds for all specifications.

In column 2 we examine how the composition of GDP—in particular, health expenditures—affects incentives to launch, controlling for overall purchasing power. Adding the log of health expenditures per GDP to the model sharply reduces the impact of GDP per capita (the implied elasticity on launch lags falls from -0.40 to -0.04), but the effect is picked up by health expenditures (elasticity on launch lags of -0.51). Importantly, the overall impacts of process and product patent regimes are generally robust to this change in the specification. However, the coefficient on the *Propatent Index* declines by about half, and the coefficient on *Short_Product* patents becomes much smaller and statistically insignificant, while *Medium_Product* patents significantly accelerate diffusion, with an impact about half the size of *Long_Product* patents. These coefficients are stable across a variety of specifications once we control for health expenditure.

[21] Taken at face value, this regression specification would also imply that the product and process effects are additive: e.g., a country with *Medium_Process* and *Long_Product* would have 32.4 + 54.5 =95 percent shorter launch lags. In fact, since the patent terms likely overlap substantially, the actual period of market exclusivity for the patent holder will be close to the longer of the patent terms, and the impact on launch lags is better estimated by the largest of the two coefficients rather than their sum.

[22] The parameter estimates are similar to those reported in Table 3. The only notable differences occur when we define long patents as $\geq$ 17 years (rather than the baseline definition $\geq$ 18). In that case, the point estimates of the coefficients on *Medium_Process* and *Long_Product* decline by about a third (though the differences are not statistically significant), and the coefficient on *Long_Process* is now positive and statistically significant.

Column 3 expands the set of controls to include the Gini index of income inequality, the fraction of elderly in the population and three health policy institutions. The key finding is that the coefficients on price regulation and patent regime variables are robust to adding these new controls. Additionally, we find that drugs are launched faster in countries with a more elderly population, and the impact is large—a standard deviation increase in the fraction of population over age 65 reduces launch lags by 21 percent. Moreover, for a given level of GDP per capita, the distribution of income is a significant determinant of market entry. Greater income *inequality* (higher Gini) increases the speed of diffusion significantly—a standard deviation rise in the Gini index reduces launch lags by 23 percent. The likely reason is that greater inequality makes it more likely that there are at least some elements in the population (the 'wealthy elite') that can afford to buy the drugs.

The health policy institutions we incorporate are whether the country has a national formulary, an essential drug list, and a national drug policy. The essential drug list and national formulary play two roles. They facilitate distribution of drugs to the population, which increases effective market size and thus promotes earlier drug launches. At the same time, they signal more effective institutions for implementing any price control regimes that may be in place, which would reduce incentives to launch. Their impact is thus an empirical question. We find that these institutions have a large and statistically significant impact on diffusion. The point estimates imply that the predicted time to launch is 31 percent lower in countries that have adopted the Essential Drug List, and an additional 16 percent lower if they have a national formulary in place.[23] Adopting a formal national drug policy has no significant impact, which may not be surprising since, although this signals policy intent, it may not be associated with any concrete implementation.[24] Unfortunately, it is not possible with the available data to unbundle these institutions and to identify the specific features that make entry more attractive. These are important policy issues but require much more detail about how these institutions actually function in different countries.

Finally, we examine the impact of the quality of regulatory screening on diffusion. If regulatory quality is correlated with the choice of patent and price control regimes, we would miss-measure the true impact of policies on diffusion speed. To address this concern, in column 4 we include a measure of bureaucratic quality for each country/year observation, taken from the World Bank. Since better screening is more likely to block launch of drugs with weaker claims to safety and efficacy, we expect to see longer average launch lags in such countries. Conversely, review which is perfunctory or driven by corruption is likely to be faster. However the impact of better screening should depend on the quality of the drug—more effective regulators are especially likely to block low quality drugs. To test this idea, we interact the measure of bureaucratic quality with dummy

[23] We stress that this is *not* the effect on launch times for drugs which are listed on the EDL. While it would be interesting to look at the diffusion rate specifically for EDL-listed drugs (given that they are considered particularly important for basic health), there were too few additions to the EDL during the sample period to do this reliably.

[24] Of course, these variables may also serve as proxies for broader institutional quality in the country, though in column 4 and all subsequent regressions we include an index of the rule of law (from the World Bank). Its estimated coefficient is rarely statistically significant, however.

variables for whether the drug was approved by the FDA (*BQ_FDA* and *BQ_nonFDA*). The estimated coefficients on the policy variables are robust to this extension. Point estimates imply that launch lags are longer for all drugs in countries with higher quality bureaucracy but, as expected, the effect is an order of magnitude larger for low quality drugs than for those approved by the FDA: a standard deviation increase in bureaucratic quality increases launch lags by three percent for FDA approved drugs, but by almost 50 percent for low quality drugs.

V. Robustness Analysis

In this section we check robustness of the main results to a variety of different specifications. In each case, we introduce the changes relative to the baseline specification given in column 4 of Table 3.

First, we introduce random drug effects to allow for unobserved drug-specific characteristics such as a drug's potential market size (e.g., differences in the incidence of the targeted diseases) or differences in the difficulty and cost of obtaining regulatory approval. These random effects enter as a multiplicative factor in the model for the hazard function, and are assumed to follow a Gamma distribution (this standard formulation yields a convenient analytical expression for the likelihood function). Overall the results, presented in column 1 of Table 4, are similar to the estimates in the baseline specification.

Second, we use a more disaggregated classification of therapeutic categories, based on the second level of the World Health Organization's ATC classification (for example, 'anti-hypertensives' as opposed to 'cardiovascular system'). The results in column 2, using 61 rather than 14 therapeutic class fixed effects, are again very close to the baseline specification.

Third, we examine whether our results for the full sample of drugs also hold when the model is estimated using only data on the subset of higher quality drugs, as represented by those that were approved by the U.S. FDA. Since these drugs may be especially important for public health, it is critical to know how policy choices affect their diffusion. In addition, an observed failure to launch may be driven by idiosyncratic variation in a country's regulatory environment, rather than by the profitability calculations as modeled in Section I. Focusing on drugs approved by the FDA, one of the world's most stringent regulatory authorities, helps rule this out.[25] The results, given in column 3, confirm that all of our main findings hold up for this subset of drugs, with point estimates very close to the those from the baseline specification for both price regulation and patent policy regimes, as well as the other covariates.

Fourth, we consider differences between high income and developing countries. Historically there has been much less variation in patent regimes in high income countries than in developing economies and there was (and remains) serious opposition to harmonization of patent policies under the TRIPS Agreement. Opponents of harmonization on a relatively long-duration and broad-based patent standard asserted then (and now) that

[25] Even if regulatory standards are low, a drug may not be launched due to specific regulatory practices that raise the cost of entry, such as a country requiring that clinical trials be conducted on its own residents before approving the drug.

the effects of patent protection are likely to be more damaging for developing countries, both because their capacity to innovate in drugs was lower (reducing any positive incentive effects from patents) and because the deleterious price effects of patent protection could fatally undermine the market for drugs in poorer countries. In column 4 of Table 4, we drop high income countries from the sample. Strikingly, the qualitative results, and most of the point estimates—in particular, the coefficients on the patent and price control policy regimes—are very similar to the baseline specification where we use all countries. The main differences are that the impact of population is smaller among lower/middle income countries, the Propatent index is no longer significant, and the relative magnitudes of the impact of EDL and national formularies are reversed. The important conclusion is that the impact of patent and price regulation policies is not confined to high income countries.

Fifth, we extend the baseline specification to allow for interactions between price regulation and patent policy regimes. The effect of patent regimes on launch incentives may not be independent of the degree of price regulation in a country. In the extreme case where price controls bring prices down to unit cost, patent protection would not provide any incentive for launch. In less extreme cases, we would expect the incentives provided by patent protection to be reduced as compared to an unregulated market. To investigate this, we interact the dummy for price regulation with the two extremes of patent regimes in our data, *Short_Process* and *Long_Product*.[26] The results in column 5 provide some evidence that price controls strongly dilute the incentive effects of patent protection. In the absence of price regulation, the point estimates of *Short_Process* and *Long_Product* on the launch hazard are both about 0.33 and highly significant. When there is strong price regulation, the impact of *Short_Process* falls essentially to zero (the estimate is -0.04, and the test on the sum of coefficients does not reject the null of zero, p-value=0.63), while for *Long_Product* it declines by about 40 percent to 0.20 but is still strongly significant (p-value <0.001). These results highlight the importance of taking the interactions between policy instruments into account in designing overall policy strategy for pharmaceuticals.

Finally, we investigate how indigenous process innovation capacity affects the timing of drug launches. Even with product patent protection, an innovator firm may not expect high enough profits to justify launching a drug in some countries. But a licensee (or, in the absence of a product patent, an imitator) with a sufficient cost advantage may be able to cover launch costs. Indeed, a common avenue for competitive entry in some countries is for indigenous firms to innovate on the drug manufacturing process—typically through expertise in chemical engineering. Our data do not unambiguously identify whether products are launched in a country by the product innovator or a competitor, so we cannot directly examine the role of competitive entry. Instead, we construct a proxy to capture local technical capacity to do process innovation, using the country's cumulated stock of patents in fields related to chemical engineering and manufacturing in each year (see the

[26]We also tried interacting price regulation with *Medium_Process* and *Medium_Product*, but these two patent regimes are highly correlated in the sample (very few countries have long product patents without long process patents), and the results were not clear-cut. We do not interact price regulation with *Short_Product* or *Long_Process* as neither of these variables entered significantly in the baseline regression.

Online Appendix for details), and test how this affects the timing of launches.

When we add this control (column 6), the estimated parameters on the patent and price control regimes and other covariates are robust. This shows that the observed policy regimes are not simply proxies for having a strong local R&D capability (which might in turn influence which policies are adopted). The point estimate on the stock of chemical patents is positive and statistically significant, indicating that countries with greater capacity for process innovation (and presumably manufacturing capability) have somewhat faster drug launches. This points to a potentially important role for indigenous entry, and highlights the need for process patent protection in countries with local technical capacity, especially where product patent rights are absent or ineffective.

VI. Endogenous Policy Regimes

In this section we address the potential endogeneity of patent and price control regimes. Previous studies have treated policy regimes as exogenous, however policy choices are outcomes of a political process, and are thus likely to reflect unobserved country-specific factors that may also affect the timing of new drug launches—e.g., variation in institutional quality and policy enforcement that affect profitability.[27] If these unobserved factors are correlated with observed policy regimes, the estimated effects will be biased. For example, firms have greater incentives to lobby for strong patent rights where entry is more profitable, which would lead us to over-estimate the effect of patent rights on the speed of diffusion. However, the endogeneity bias can also go the other way—countries with weak enforcement may be more willing to adopt the appearance of strong patent rights, inducing negative covariance of patent rights with the disturbance and thus a downward bias.. However, patent reform is often a condition of entry into new political groups (e.g., joining the European Union), and international trade agreements such as TRIPS (Sell (2003)), and thus arguably exogenous. This is less likely to apply to price controls, where governments typically have greater flexibility.

We begin by testing the null hypothesis that various policy regimes are independent of the error term in the launch equation, using the Rivers and Vuong (1988)approach. The tests strongly rejects exogeneity both for price controls and the process patent and product patent regimes (p-values$<$0.001).[28] In view of these tests, we adopt two identification strategies to address endogeneity. The first exploits within-country changes in policy regimes to identify the effects of interest. A significant number of countries changed patent and/or price control regimes at least once during the sample period, and 15-40 percent of total variance in the policy variables is in the within-country dimension

[27] Reverse causality—where launch lags drive regime choice—is hard to rationalize in our context. Regime choice might be negatively correlated with *past* launch lags—long delays might induce governments to introduce more attractive policy regimes—but whether this induces endogeneity bias depends heavily on the assumed structure of errors in the launch and regime choice equations.

[28] We first estimate regressions for the choice of policy regimes, including all controls from the baseline specification of the hazard model plus a set of instrumental variables described in the text below (we conduct the tests both using the narrow and broad instrument sets). We use a Probit for price controls and Ordered Probits for the short, medium and long process and product patent regimes. The instruments are jointly significant in these policy choice regressions (p-values $<$0.001). The generalized residuals from these regressions are added to the hazard model, and exogeneity is tested by the significance of the coefficients on the associated generalized residuals.

(see Table A.2 in the Online Appendix.) *If* the unobserved heterogeneity is constant over time for a given country, introducing country fixed effects into the hazard model will deliver consistent estimates.

However, it seems quite likely that these unobserved factors might evolve over time, in which case the fixed effects approach will not provide consistent estimates of the policy effects. To allow for this possibility, we adopt a second approach based on instrumental variables. This approach requires instruments that are correlated with policy choices but do not directly affect the timing of drug launches (and are plausibly uncorrelated with unobserved heterogeneity). In the estimates presented below we use various sets of instruments based on measures of a country's political institutions, legal system and ethnolinguistic diversity (which are unlikely to affect drug launches) and the number of regional trade agreements it has entered (which we include as a proxy for pro-market orientation of a country's institutions).[29] The Online Appendix provides details of variables and sources.

We implement both these approaches using a semiparametric specification of the hazard function (Lillard (1993)) that allows for a flexible form of the baseline hazard, as well as implementation of an IV approach using FIML joint estimation of the hazard equation with 'first stage' equations that model policy variables as a function of the instruments. In this setup, we introduce correlation between the disturbances in the launch and policy regime equations by adding a common random country effect in each equation.[30]

Table 5 summarizes parameter estimates for the policy variables in the hazard equation (the coefficients on control variables are not reported, for brevity). Column 1 is the baseline hazard model using this semiparametric specification—the estimates are very similar to those from the Weibull specification.[31] In column 2 we allow for country *random effects*, and obtained estimated coefficients on most of the policy variables which are very similar to the estimates in column 1. The estimates in column 2 confirm that the differences between the IV estimates (presented next) and the baseline estimates are not due to the inclusion of the country random effect. In column 3 we introduce country *fixed effects*, identifying the policy effects off the time series variation in launch lags within countries (column 3).[32] A Hausman test strongly rejects the random effects specification against the alternative of fixed effects, which confirms that the unobserved factors are

[29] If trade openness makes markets more profitable to enter, there could be correlation between the regional trade agreement instrument (RTA) and the error term in the launch equation. However, the IV results presented below show that the parameter estimates are robust to whether or not RTA is included in the instrument set.

[30] In the absence of such correlation, the regimes would not be endogenous in the launch equation (which the Rivers-Vuong test rejected). We adopt the Lillard framework because we were unable to get nonlinear GMM estimation with the Weibull model to converge. With time-varying covariates, the data form a large unbalanced panel in which each observation in the GMM objective function (observed launch status minus predicted in the final period) is conditional on the entire history of each drug-country up to the last period observed, making the selection of valid instruments very challenging.

[31] The duration-dependent part of the hazard function is modeled using year dummies for $t \in [0, 9]$ and $t > 9$. Estimated coefficients on these time dummies imply a pattern of duration dependence consistent with a Weibull distribution with slope parameter of about 0.6, through to about 12 years.

[32] To avoid computational problems in this non-linear context, covariates that are essentially fixed over time were dropped. The criterion we use is whether within-country variation accounts for less than 5 percent of the total). The variables dropped are population, GDP per capita, health expenditures per GDP, Gini, and fraction of the population over 65.

correlated with observed policy regimes (p-value $< .001$).

Overall, the estimates confirm that price controls and, with some qualification, patent policies significantly affect the timing of drug launches. The parameter estimates for price controls, short and medium duration process patents, and long product patents are actually *larger* than the baseline specification which treats policy regimes as exogenous, indicating a negative endogeneity bias. As before, we find no significant effect of short product patents, however the coefficient on long process patents turns negative and significant, the coefficient on medium product patents loses significance and the Propatent index is negative and significant. Note, however, that these fixed effects estimates are consistent only under the rather strong assumption that the unobserved country-level heterogeneity is constant over time, which we believe is unlikely, and these anomalous results are reversed when we use instrumental variables, which we turn to next.

To account for the possibility of time-varying, correlated heterogeneity, in columns 4 and 5 we present the FIML (IV) estimates using two sets of instruments.[33] In the first model we use a minimal set of instruments which contains measures of two important aspects of a country's political institutions: *Political_Constraints*, which measures the degree to which voting rights within the political structure constrains policy change, which is used in the political science literature as a proxy for credible policy commitment; and *Executive_Orientation*, coded as a right, left or center party with respect to its orientation on economic policy. In the second model, we expand the instrument set by including: *Ethnolinguistic_diversity*, commonly used in the economics and political science literature as an indicator of difficulty in reaching and committing to political decisions; *Legal_Origin* which coded as common law, French law, German law, or Socialist/Other; and *RTA* which is the cumulative number of regional trade agreements that the country has entered. Very similar results were obtained without *RTA*, and for other combinations of these instruments.

Three main conclusions stand out. First, as with country fixed effect regressions, the coefficients on price controls and patent regimes are generally *larger* than those obtained when the policy regimes as treated as exogenous. If endogeneity were driven by unobserved heterogeneity in the profitability of markets, we would expect an upward bias. To the contrary, our findings suggest that the endogeneity bias is more consistent with negative correlation between the adoption of strong policy regimes and unmeasured aspects of political and legal institutions, such as enforcement of patent rights. Second, the pattern of policy impacts is similar to what we found in the earlier regressions. Process patents raise the hazard of launch (i.e., reduce launch lags), and the impact increases with the duration of such patents. Note in particular that the negative effect of long process patents found in the fixed effects specification is reversed here. Again, as before, we find that *Medium_Product* and *Long_Product* have large impacts on launch lags, while short product patents have little effect. Third, the estimates are generally similar using both the narrow and broader sets of instruments (the main exception is the coefficient on short process patents in column 5.)

[33] Details of the parameter estimates for the policy regime equations are provided in the Online Appendix.

VII. Policy Simulations

In this section we illustrate how different policy choices affect the speed of drug diffusion. The metric we adopt is the predicted time it takes for 25 percent of drugs to be launched (*LAG25*) under different counterfactual policy regimes. Using our estimated parameters, we solve for the value of the 25th percentile of the estimated 'failure' function for each drug/country observation, conditional on covariates, and then examine the median value across observations.[34] We begin with a benchmark computation of *LAG25* for a regime with no patent protection or price regulation, and then introduce three counterfactual policy regimes: short process patents, long product patents, and price controls. Table 6 shows results both for all drugs and the subset of FDA approved drugs, and then for low, middle and high income countries.

Panel A of Table 6 is based on the baseline Weibull regression estimates from column 4 of Table 3 which, as discussed in the previous section, likely underestimate the impact of policy choices on launch lags. The results further confirm our descriptive findings that diffusion of new drugs is slow, and varies across drug and income categories.[35] In the benchmark case with no patents or price controls, it takes 4.63 years for 25 percent of drugs to be launched in the pooled sample. This falls to 3.01 years for FDA approved drugs, which is good news from a welfare perspective. But there is substantial variation across income categories—the median lags are more than three times longer in low income countries (8.85 years) as compared to high income countries (2.60 years).

Setting the patent regime to short process patents only (i.e., *Short_Process* =1 and price controls and all other patent variables =0) reduces predicted launch lags by about 25 percent. Slightly shorter launch lags are estimated for a regime with no process patents but long product patents (and no price controls). Introducing price controls in a regime with no patents increases lag times by 29 percent above the benchmark. Recall that given the functional form of the baseline empirical model, the percentage effects of these policy regimes are additive: thus introducing both price controls and long product patents generates a predicted median value of *LAG25* of 4.09 years. In other words, price regulation removes most of accelerated diffusion induced by long product patents.

Panel B presents the median predicted launch lags when we use the FIML parameter estimates on the policy variables, which take into account the endogeneity of policy regimes.[36] Using these coefficients, product patents emerge as much more effective than process patents (69 percent reduction in launch lags compared to 29 percent), and price regulation has a very large impact, more than doubling launch lags.

In both panels, the same pattern of results holds for the subset of FDA approved drugs, and for low, middle, and high income countries. In low income countries, *LAG25* is

[34] To do this, we set the values of the time-varying covariates at their sample means (over time) for each drug/country observation. We focus on the median value of $LAG25$ because many drugs are never launched in a number of countries, so the distribution of $LAG25$ is sharply skewed.

[35] Although similar to the numbers in Table 2, note that these figures are not directly comparable since they control for economic and demographic variables, drug therapeutic class, and set the patent and price controls policy variables to counterfactual values.

[36] Specifically we recompute the predicted launch lags from the Weibull model after substituting the coefficients on the patent and price controls variables with values from the FIML estimates in column 4 of Table 5.

depressingly high in the benchmark case, at almost nine years. Notice that, based on these results, a policy regime directed solely at lowering prices on drugs that have been already been launched (no patents, and strong price controls) would increase launch lags very substantially to over three times longer than in a 'pro-innovator' regime with no price controls and long product patents.

Several qualifications should be kept in mind. First, these calculations are not a welfare assessment of different regimes—this would require, at a minimum, consideration of how these policies affect drug prices. This is difficult unless one can model both the demand side—as a practical matter, this requires restricting the analysis to specific classes of drugs (e.g., Chaudhuri, Goldberg and Gia (2006))—and the supply side, i.e., the investment required for launch. One would also need to address how to evaluate the relative welfare gains from incremental versus radical innovation in this context. *If* gains associated with increased product variety and incremental quality improvements were relatively small, and *if* policy regimes primarily affected diffusion of such follow-on products, the overall welfare impact might not be as severe as Table 6 suggests.

Second, because our empirical model is not structural, counterfactual assessment of policies is subject to the Lucas critique, among other issues. A third, related, point is that countries develop institutions and invest in human capital over long time periods, and in ways that both influence, and in turn are influenced by, the policy regimes they adopt. Thus there may be important path dependencies driving observed outcomes—and the estimated policy impacts shown here may take many years to unfold. Any assessment of a new policy regime needs to take into account the capacity of the country to adapt and the costs of doing so.

VIII. Concluding Remarks

This paper studies how patent rights and price regulation affect launch lags for new drugs. Using new data on launches of 642 new molecules in 76 countries during 1983-2002, we show that, all else equal, longer and more extensive patent protection strongly accelerated diffusion, while price regulation delayed it. Health policy institutions, and economic factors that make markets more profitable, also sped up diffusion. These results hold both for developing countries and high income countries, and the results are robust to using instrumental variables and country fixed effects to address the endogeneity of policy regimes.

Of course, the same policies that promote faster launch—stronger patent rights and the absence of price regulation—are also those that raise prices. This highlights the basic tradeoff countries face between making new drug therapies available and making them affordable. Finding ways to mitigate the adverse effects of this tradeoff remains a major challenge. One possible approach would be to introduce multilateral recognition of drug trials and regulatory approval, lowering launch costs and speeding up global drug diffusion. Finally, our findings highlight the broader point, not limited to pharmaceuticals, that patent rights can have an important impact on the *diffusion* of new innovations as well as on the rate at which new innovations are created.

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TABLE 1—GEOGRAPHIC SCOPE OF DIFFUSION OF NEW DRUGS

		Percent of Drugs Launched		
No. of countries	No. of Drugs	All Drugs	FDA Approved	FDA Priority Reviewed
1-3	145	23	13	13
4-10	101	16	12	10
11-25	133	21	20	16
26+	263	41	55	62

Note: Table shows the number of countries in which each drug is launched during the period 1983-2002, with no adjustment for censoring of launch lags or for changes in the number of countries present in the data.

TABLE 2—SPEED OF DIFFUSION OF NEW DRUGS

	(a) Fraction launched within 10 years (percent)			(b) Time by which 25 percent launched (years)		
	All Drugs	FDA Approved	FDA Priority Reviewed	All Drugs	FDA Approved	FDA Priority Reviewed
Income Level						
Low Income	27.1	34.3	39.4	8.98	6.99	5.99
Middle Income	39.1	50.4	50.7	4.05	3.01	2.99
High Income	46.5	61.0	63.4	2.01	1.97	1.02
Patent Regime						
None	29.5	43.4	39.5	7.99	4.02	4.01
Short	33.9	42.9	43.1	6.00	4.42	3.99
Medium	35.2	47.3	47.0	5.43	3.99	3.98
Long	45.9	58.1	60.6	2.56	1.99	1.45
Price Regulation						
Weak/None	44.0	56.4	58.4	2.99	1.99	1.97
Strong	37.4	49.1	50.1	4.98	3.06	3.01
Overall	41.3	53.5	55.3	3.41	2.45	2.00

Note: Table entries are based on the estimated Kaplan-Meier survivor function, which adjusts for censoring of launch lags. Countries are categorized as Low, Middle, or High income based on the World Bank's categories and their GDP per capita at PPP in 2001. Based on 298,605 observations. FDA Approved subsample has 163,853 observations, and the FDA Priority Reviewed subsample 64,778.

TABLE 3—WEIBULL MODEL OF DRUG LAUNCH: PROPORTIONAL HAZARD COEFFICIENTS

	(1)	(2)	(3)	(4)
Elapsed time	0.614**	0.618**	0.611**	0.611**
	(0.006)	(0.006)	(0.006)	(0.006)
Price Controls	-0.153**	-0.171**	-0.140**	-0.153**
	(0.018)	(0.018)	(0.019)	(0.019)
Short_Process	0.117	0.175**	0.180**	0.179**
	(0.065)	(0.066)	(0.067)	(0.067)
Medium_Process	0.199**	0.171**	0.159**	0.164**
	(0.053)	(0.053)	(0.055)	(0.055)
Long_Process	0.017	0.031	0.004	0.053
	(0.063)	(0.059)	(0.060)	(0.060)
Short_Product	0.130*	0.020	-0.064	-0.019
	(0.065)	(0.066)	(0.066)	(0.066)
Medium_Product	0.077	0.174**	0.142**	0.130**
	(0.042)	(0.041)	(0.042)	(0.042)
Long_Product	0.335**	0.303**	0.260**	0.229**
	(0.058)	(0.054)	(0.054)	(0.055)
Propatent Index	0.372**	0.169**	0.154**	0.220**
	(0.051)	(0.052)	(0.054)	(0.056)
Log(population)	0.074**	0.076**	0.077**	0.083**
	(0.007)	(0.007)	(0.007)	(0.007)
Log(GDP/cap)	0.247**	0.023	0.015	0.048*
	(0.015)	(0.018)	(0.020)	(0.023)
Log(Health/GDP)		0.313**	0.259**	0.275**
		(0.017)	(0.018)	(0.018)
FDA Approved drug	1.357**	1.375**	1.355**	0.540**
	(0.024)	(0.024)	(0.025)	(0.065)
Gini Coefficient			0.014**	0.012**
			(0.001)	(0.001)
% Pop Age 65+			0.026**	0.024**
			(0.003)	(0.003)
BQ* FDA drugs				-0.001
				(0.001)
BQ* non-FDA drugs				-0.012**
				(0.001)
Rule of Law index				0.001
				(0.011)
National Drug Policy			0.028	0.009
			(0.032)	(0.032)
Essential Drug List			0.189**	0.204**
			(0.032)	(0.033)
National Formulary			0.098**	0.093**
			(0.027)	(0.027)
ATC Dummies	YES	YES	YES	YES
No. Observations	298,605	298,605	298,605	298,605
log-likelihood	-45,413	-45,237	-45,122	-45,034

Note: * significant at 5 percent and ** significant at 1 percent. Standard errors clustered on country-drug in parentheses.

TABLE 4—WEIBULL MODEL OF DRUG LAUNCH: ROBUSTNESS ANALYSIS.

	(1) Drug Random Effects	(2) Level 2 Therap. Class Effects	(3) FDA Approved drugs	(4) Low/ Middle Income	(5) Interactions of Patents with Price Controls	(6) Local Innovation Capacity
Price Controls	-0.214**	-0.157**	-0.181**	-0.205**	-0.040	-0.147**
	(0.020)	(0.019)	(0.021)	(0.029)	(0.037)	(0.019)
Short_Process	0.185**	0.168*	0.134	0.172*	0.325**	0.171*
	(0.068)	(0.067)	(0.075)	(0.079)	(0.073)	(0.067)
Medium_Process	0.138*	0.163**	0.140*	0.188**	0.174**	0.156**
	(0.057)	(0.054)	(0.061)	(0.062)	(0.055)	(0.055)
Long_Process	0.019	0.049	0.037	0.034	0.025	0.046
	(0.062)	(0.060)	(0.066)	(0.068)	(0.061)	(0.061)
Short_Product	-0.023	-0.006	-0.048	-0.017	-0.015	-0.028
	(0.067)	(0.066)	(0.073)	(0.076)	(0.066)	(0.066)
Medium_Product	0.175**	0.144**	0.112*	0.064	0.144**	0.131**
	(0.044)	(0.041)	(0.046)	(0.047)	(0.042)	(0.042)
Long_Product	0.279**	0.239**	0.191**	0.241**	0.328**	0.232**
	(0.057)	(0.054)	(0.059)	(0.074)	(0.061)	(0.055)
Short_Process x Price Controls					-0.368**	
					(0.080)	
Long_Product x Price Controls					-0.124**	
					(0.043)	
Propatent Index	0.370**	0.229**	0.231**	-0.036	0.220**	0.187**
	(0.054)	(0.055)	(0.061)	(0.096)	(0.055)	(0.057)
Stock of Chemicals Patents						0.014**
						(0.005)
log-likelihood	-38,903	-43,681	-35,101	-20,602	-45023	-45030

Note: * significant at 5 percent and ** significant at 1 percent. Standard errors clustered on country-drug in parentheses. 298,605 observations, except for columns 3 and 4 which have 163,853 and 168,684 observations respectively. All equations also include the other explanatory variables in column 4 of Table 3.

TABLE 5—HAZARD MODEL OF DRUG LAUNCH WITH ENDOGENOUS POLICY REGIMES

	(1) Baseline	(2) Country Random Effect	(3) Country Fixed Effects	(4) IVs: Political Constraints, Executive Orientation	(5) + Ethno-Linguistic Diversity, Legal Origins, No. of RTAs
Price Controls	-0.155**	-0.189**	-0.181**	-0.491**	-0.566**
	(0.020)	(0.023)	(0.042)	(0.025)	(0.026)
Short_Process	0.143**	0.151**	0.284*	0.211**	0.098
	(0.065)	(0.074)	(0.186)	(0.067)	(0.068)
Medium_Process	0.121**	0.105*	0.193**	0.344**	0.269**
	(0.053)	(0.057)	(0.076)	(0.053)	(0.051)
Long_Process	0.026	-0.118	-0.287**	0.431**	0.313**
	(0.053)	(0.078)	(0.089)	(0.059)	(0.059)
Short_Product	-0.032	0.021	0.148	0.031	0.009
	(0.065)	(0.075)	(0.225)	(0.068)	(0.068)
Medium_Product	0.156**	0.142**	0.051	0.425**	0.362**
	(0.041)	(0.044)	(0.066)	(0.041)	(0.040)
Long_Product	0.173**	0.311**	0.461**	0.721**	0.639**
	(0.054)	(0.065)	(0.078)	(0.051)	(0.054)
Propatent Index	0.147**	0.164**	-0.230	0.211**	0.170**
	(0.056)	(0.068)	(0.129)	(0.058)	(0.057)
log-likelihood	-90,666	-86,631	-90,058	-605,230	-585,949

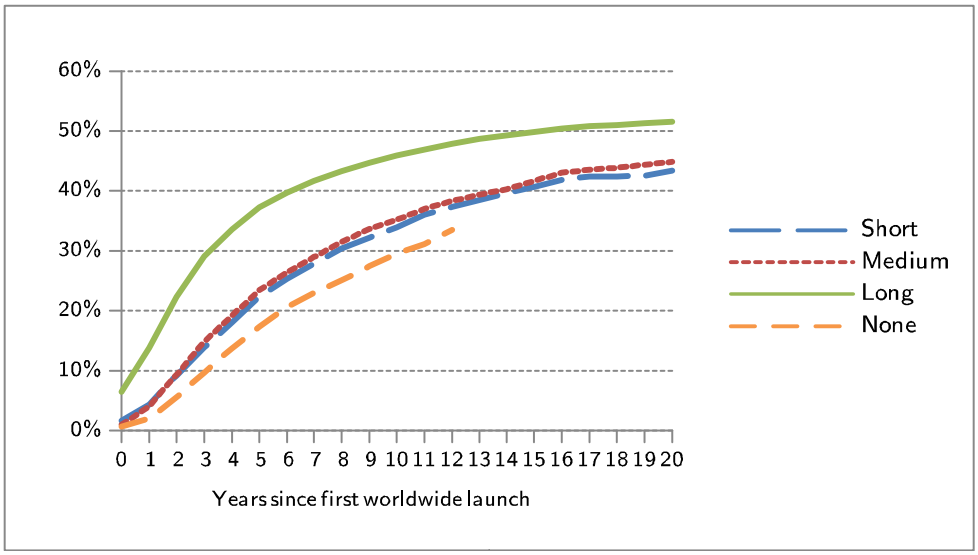
Note: * significant at 5 percent and ** significant at 1 percent. Standard errors clustered on country-drug in parentheses. 298,605 observations, except for columns 3 and 4 which have 163,853 and 168,684 observations respectively. All equations also include the other explanatory variables in column 4 of Table 3.

TABLE 6—IMPACT OF POLICY REGIMES ON LAUNCH LAGS

	All Drugs	FDA Approved drugs	Low income countries	Middle income countries	High income countries
Benchmark	4.63	3.01	8.85	4.91	2.60
Panel A: Median lag to predicted 25 percent diffusion using baseline coefficients					
Regime 1: Short_Process	3.45	2.25	6.61	3.67	1.94
Regime 2: Long_Product	3.18	2.07	6.09	3.38	1.79
Regime 3: Price controls	5.95	3.87	11.38	6.31	3.35
Panel B: Median lag to predicted 25 percent diffusion using FIML coefficients on policy variables					
Regime 1: Short_Process	3.28	2.13	6.27	3.48	1.84
Regime 2: Long_Product	1.42	0.93	2.72	1.51	0.80
Regime 3: Price controls	10.34	6.73	19.77	10.98	5.82
No. observations	38,180	26,319	3,350	17,976	16,854

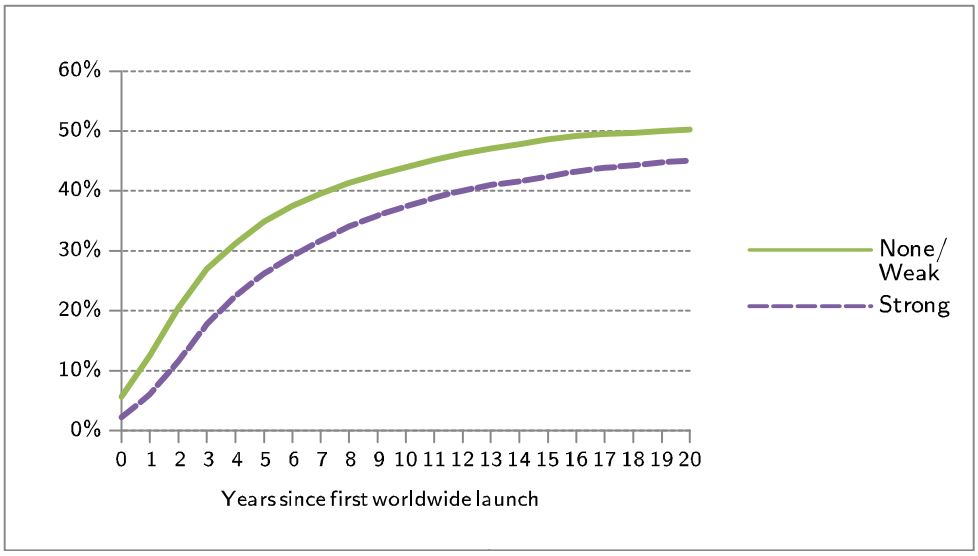
Note: Table entries are median values of 38,180 drug-country observations on the 25th percentile of the estimated Weibull failure function. In Panel A the parameters for this calculation are the estimated coefficients from the Weibull model in Table 3, column 4, and in Panel B they are the estimated coefficients on policy variables from Table 5, column 4.

FIGURE 1. FRACTION OF DRUGS LAUNCHED BY PATENT REGIME



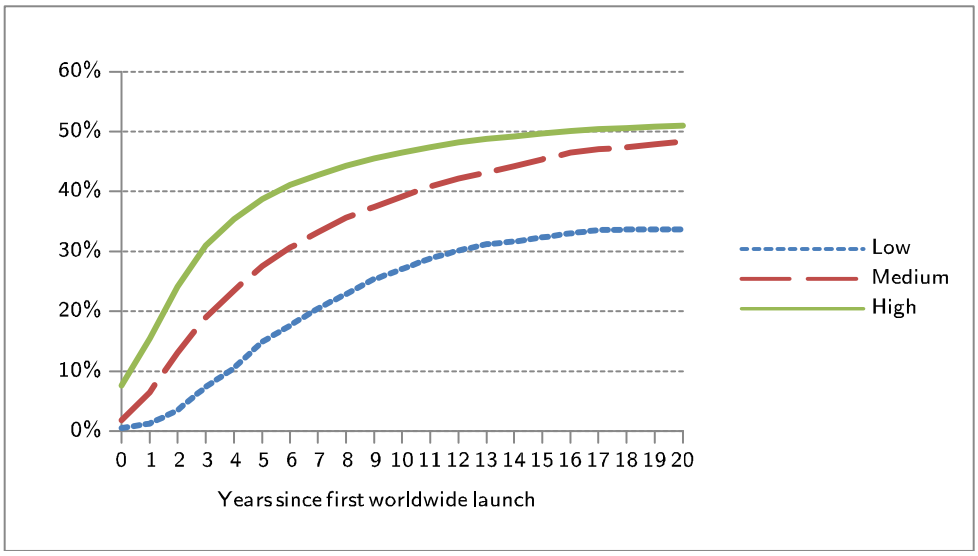
Note: Figure plots the Kaplan-Meier failure function for drug launches by patent regime, showing the fraction of drug-country launch opportunities filled against time since first worldwide launch.

FIGURE 2. FRACTION OF DRUGS LAUNCHED BY PRICE CONTROL REGIME



Note: Figure plots the Kaplan-Meier failure function for drug launches by price control regime, showing the fraction of drug-country launch opportunities filled against time since first worldwide launch.

FIGURE 3. FRACTION OF DRUGS LAUNCHED BY INCOME



Note: Figure plots the Kaplan-Meier failure function for drug launches by country income group, showing the fraction of drug-country launch opportunities filled against time since first worldwide launch.

Online Appendix:
Patents and the Global Diffusion of New Drugs

Iain M. Cockburn and Jean O. Lanjouw and Mark Schankerman

Data Sources and Construction

New Drug Launches

The phenomenon of interest here is the dating of the launch of each new drug in each country. This was derived from the dating of launches of drug products, which contain the new drug, in combination with inactive ingredients and potentially other active ingredients. The distinction between `drug' and `drug product' is significant. Not all new drugs are launched as exactly the same product in all countries. A given `active moiety' may be approved as different salts or esters in different countries (as sulfate, hydrochloride, maleate etc.) or in different galenical forms (tablet, injectable, topical cream etc.), or may be sold in combination with different sets of other active ingredients.

Drug launches were identified from two sources of data, in which the unit of observation is a drug product. The first is the December 2002 version of the *LifeCycle: Drug Launches* database obtained from IMS Health, Inc. This file contained 187,725 observations on retail drug product launches for the period 1982-2002. The unit of observation is product-country-year, with each observation recording: (1) the trade name (proprietary product name, or brand name); (2) a listing of active ingredients using non-proprietary generic chemical name; (3) the composition, listing the formulation (capsule, syrup, powder etc.) and amounts, strength or concentration of the active ingredient(s); (4) the date the product goes on sale; and (5) the therapeutic class of the product using the World Health Organization's Anatomical Therapeutical Chemical classification system at the third level. This database covers all therapeutic classes, but not all countries. Coverage of countries increased over time, with product launches observed in 45 countries in 1982, increasing to 66 in the early 1990s, and to 76 by the end of the sample. In two cases country was coded by IMS as a region: French West Africa, consisting of Benin, Cameroon, Congo, Cote d'Ivoire, Gabon, Guinea, and Senegal; and Central America consisting of Costa Rica, El Salvador, Guatemala, Honduras, and Panama. Notably, India was not included in this database during this period.

The drug launch data for India were obtained from a second source, the *FirstIndia* dataset of product sales compiled by ORG MARG, a market research company. This covers the period 1967 to 1997 but only for a partial set of therapeutic classes, namely antibiotics, cancer, and antiulcer. This dataset contained 498 observations on brand name, active ingredient(s), therapeutic class, and launch date.

Identifying drug launches in these data consistently across countries and over time was a significant challenge. In the data, 14 percent of records had no listing of active ingredients, only a brand name, for about one fifth of which the active ingredient could be recovered through lookup of the brand name or through parsing of the composition field. Moreover, 24 percent of records were for multi-ingredient or combination products: in some cases more than 20 ingredients were listed. About 20 percent of products fell into categories in which active ingredients were prohibitively difficult to identify consistently (vaccines, biologics, hormones, allergens, immune globulins etc.), appeared to be for non-prescription

products such as nostrums, over-the-counter, or proprietary formulations, herbal and homeopathic medicines, or were for `non-drug' medical products, such as blood-testing strips, imaging contrast agents, non-medicinal or inactive ingredients or excipients, diagnostics, and surgical solutions.

As a preliminary step, we therefore excluded 17,452 records for products whose ingredients could not be identified. After a very careful effort to identify brand names of known drugs, we believe that no instances of launches of new drugs were excluded for this reason. We further excluded 37,199 records in therapeutic classes largely populated with non-prescription or hard to identify products,[1] and 2,274 records for vaccines.

Remaining records were `unpacked' to give one observation per ingredient per product, with the exception of 29 combination drugs given a distinct non-proprietary name in the British Pharmacopeia where ingredients were combined.[2] This created an additional 29,784 observations, and was done to be `over-inclusive' in identifying drug launches: while many drug products combine active ingredients, treating all combinations of new and old chemical entities as distinct products would result in spuriously high counts of new products, and under-identification of launches of new entities.

In principle each active ingredient is unambiguously identified by the generic name, in practice these are not fully standardized, or may use spelling variations from different languages, or may not have been assigned. After excluding non-drug or hard-to-identify products and ingredients, we observe 9,065 distinct active ingredients in the remaining 115,123 observations on country and ingredient. The great majority of these compounds were not directly relevant to this study, since they were first introduced before 1983, or are nonprescription drugs such as aspirin. Considerable effort was nonetheless invested in coding this list of active ingredients consistently, to avoid miss-identification of drugs and consequent under-identification of drug launches. A variety of online and hardcopy reference sources were consulted, including: the *ChemIDplus* database maintained by the US National Library of Medicine, the *WHO-MedNet* database, the University of Alberta *DrugBank* database, the *DrugBase* database published by Wissenschaftliche Verlagsgesellschaft Stuttgart, the Health Canada *Non-Medicinal Products Database*, the FDA's *Inactive Ingredients Database*, the Kyoto University and University of Tokyo *KEGG DRUG* database, and current and historical editions of the *Martindale Complete Drug Reference* published by The Pharmaceutical Press, the *Merck Index*, the *Index Nominum* published by the Swiss Pharmaceutical Society, and the *USP Dictionary of United States Adopted Names (USAN) and International Drug Names*

[1] Products in the following therapeutic classes: toothpaste and dentifrices, digestives, vitamins, mineral supplements, tonics, laxatives, anti-anemics, topical antihaemorrhoidals, certain dermatologicals (emollients and protectives, wound and ulcer preps, anti-pruritics, disinfectants, medicated dressings, acne, miscellaneous), parenteral nutrition, bacterial immunostimulants, smoking cessation, herbal cough and cold, ophthalmics, otologicals, allergens, herbal and homoeopathic medicines. These were identified through the ATC codes (A1A, A9, A11, A12, A13, A6, B3A, B3B, C5A, D2, D3, D4, D8, D9, D10, D11, K, L3X, N7B, R5F, S, T, V) or through manual examination. Vitamins and non-prescription or OTC drugs were identified from reference sources such as the *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements*. Herbal and homeopathic products were identified by hand inspection, lookup in *Physicians' Desk Reference for Herbal Medicine*, or being manufactured by a company specializing in herbal products e.g. Arkopharma, Weleda.

[2] These are the drug combinations with demonstrated synergistic effects: co-amoxiclav, co-amilofruse, co-amilozide, co-amoxiclav, co-beneldopa, co-bucafapap, co-careldopa, co-climasone, co-codamol, co-codaprin, co-cyprindiol, co-drydamol, co-erynsulfisox, co-fluampicil, co-flumactone, co-hycodapap, co-methiamol, co-oxycodapap, co-phenotrope, co-proxamol, co-simalcite, co-spironozide, co-tenidone, co-tetroxazine, co-triamterzide, co-trifamole, co-trimazine, co-trimoxazole, and co-zidocapt.

published by the U.S. Pharmacopeial Convention. When possible, generic chemical names were matched to the WHO's listing of International Nonproprietary Names (INNs); when an INN was not available, the USP USAN, British Approved Name, or Japanese Approved Name was used.

As a further measure to avoid under-identification of country launches, the parts of active ingredient names corresponding to salts, esters or non-covalent derivatives were removed to arrive at the `active moiety'. This corresponds roughly to the New Chemical Entity in U.S. usage. Treating different salts, esters and derivatives as distinct entities would result in a significantly larger number of new drugs. For each of the 2,265 such chemical entities in the source dataset we determine the first worldwide launch date, based on the earliest of (1) the first date it appears in the IMS or ORG MARG datasets, (2) the first date it appears in the FDA's drugs@fda approvals database, (3) the first date it was listed as approved for marketing in any country in the *Pharmaprojects* database compiled by PJ Publications. To avoid problems with left-censoring of launch dates in 1982 in the IMS data, we exclude any drugs for which the first worldwide launch date defined this way was before 1983. We also exclude drugs that were only launched in Japan and Taiwan and/or Korea, which appear to reflect medical practice idiosyncratic to this region. This leaves us with 642 drugs, for which we observe 17,189 drug-country observations on the timing of launches.

To prepare this dataset for survival analysis, we use the first worldwide launch date to determine t=0 for each molecule, and then for each drug-country combination create annual observations for the time-varying and non-time varying covariates described below for each year until either the drug is launched in that country or is censored. Care was taken to exclude country-years where a drug was not at risk of launching (as observed in these data), for example if data were not reported for that country until after the first worldwide launch date, or if the drug were in a therapeutic class not covered in these data for that country, for example anti-hypertensives in India. This gives a total of 298,605 observations on 38,180 drug-country combinations, with the launch date censored for 20,991 drug-country combinations.

Collectively, these choices about data construction result in a data set which differs from that in Kyle (2006) and Kyle (2007), making exact comparisons difficult to draw. Kyle's studies cover a similar time period to ours (1980-2000 whereas as we use 1983-2000), but use a different source for data on launch status (the *Pharmaprojects* database) and focus on smaller sets of countries: the G7 in Kyle (2006) and 28 countries, largely the membership of the OECD, in Kyle (2007), compared to our 76 countries. The exact basis for determining launch status in the *Pharmaprojects* database is unclear, but appears to be primarily regulatory approvals, whereas IMS combines regulatory approvals, announcements by manufacturers, local media reports, and active surveillance of distribution channels announcements to determine when a product becomes commercially available. Kyle uses a significantly narrower product definition, with over 1400 distinct new chemical entities appearing her data sets compared to our 642 more broadly defined drugs, and also defines markets as drug-country-therapeutic class combinations where we look at broader drug-country tuples. Overall, we observe a similar rate of entry to that reported by Kyle, with 4.8 percent of 298,605 opportunities filled in our sample compared to 3.9 percent of 86,755 drug-country-class-year opportunities in Kyle (2006) and 2.5 percent of 299,567 opportunities in Kyle (2007). Within the same sets of countries, our broader market definition results in entry rates that, although still quite low, are roughly double those reported by Kyle: 6.9 percent of opportunities filled for the G7 and 5.7 percent for the 28 countries in Kyle (2007).

Explanatory variables

Patent Protection

We construct measures of the availability and duration of patent protection for (a) pharmaceutical products and (b) chemical processes, which are is coded for each country-year, along with presence of enforcement mechanisms.

Two sources were used. Data compiled by Ginarte and Park (1997) and Park (2008) who give dummy variables coded every 5 years 1960-2000 for up to 120 countries on (1) Coverage---i.e., availability of patent protection for different classes of subject matter, here the relevant category is chemicals and pharmaceuticals, process and product; (2) patent term, measured as years from filing or years from grant; (3) treaty membership in PCT, Paris Convention and UPOV; and (4) presence of various enforcement mechanisms and other factors impacting the scope of rights, such as preliminary injunctions, requirements to work, contributory infringement, compulsory licensing etc. This information was cross-referenced against the text of relevant statues and treaties, published in *World Patent Law and Practice: Patent Statutes, Regulations, and Treaties* by John P. Sinnott and William J. Cotreau (New York: M. Bender, 1974, seriatim), and *Patents Throughout the World*, an annually updated looseleaf publication (New York: West Group). *The Statutes, Regulations, and Treaties* information is taken as definitive regarding dating of changes in patent term, coverage of pharmaceuticals and chemical processes, patent term extensions, duration of term for foreign versus domestic applicants, and provides some ability to back fill the Ginarte-Park data to identify more precisely changes in the patent regime. There are occasional inconsistencies and conflicts between national law and multinational treaties such as the Andean Pact, the Bangui Agreement etc. In these cases, the provisions of the national law are taken as definitive.

Using these data we define: *Patent_Term* = Max(Years from grant +2, Years from filing). The distribution of country/year observations by patent term is as follows:

Patent_Term	0	3	7	10	12	14	15	16	17	18	19	20	22
No. obs	9	17	21	77	59	15	83	35	175	39	38	694	12

Using the patent term, we define the following process and product patent regimes:

- *Short_Process*=1 if chemical processes patentable and 0<*Patent_Term* ≤12
- *Short_Product*=1 if pharmaceutical products patentable and 0<*Patent_Term* ≤12
- *Medium_Process*=1 if chemical processes patentable and 13≤*Patent_Term* ≤17
- *Medium_Product*=1 if pharmaceutical products patentable and 13≤*Patent_Term*≤17
- *Long_Process*=1 if chemical processes patentable and *Patent_Term*>17
- Lo*ng_Product*=1 if pharmaceutical products patentable and *Patent_Term*>17

Propatent Index = sum of dummies for whether:

a. patent term is the same for domestic and foreign applicants
b. preliminary injunctions are available

c. infringer can be liable for contributory infringement
d. burden of proof of infringement is reversed for process inventions
e. patents cannot be revoked for failure to work
f. there is no requirement to work the patent, or can be satisfied by importation
g. there is no compulsory licensing
h. term extensions are available for pharmaceuticals

Price Controls

Each country's price control regime was coded as None/Some/Extensive from the sources listed in Lanjouw (2005). The designation `Some' means that the country has formal price control regulation but it covers only a subset of drugs. `Extensive' means that the regulation covers most drugs and/or is viewed in the sources as particularly restrictive. In the regressions a dummy variable for price control regime = Extensive is used.

Demographic and Income Variables

Age distribution: For each country-year, the total population, and percentage of the population over 65 years old are taken from the World Bank, *World Development Indicators*. We also used the percentage of the population under 5 years old, but found no effect in the regressions.

Income per capita: For each country, annual values of real GDP per capita (RGDPCH) are taken from the Penn World Table version 6.2

Income inequality: We use the Gini coefficient as reported in the World Bank's *World Development Indicators*. Since there are rarely more than two observations per country 1975-2005, missing values are interpolated using first-observation-carried-back for years prior to the first observed value, and then last-observation-carried-forward subsequently.

Health care expenditures: For each country, total health care expenditure as percent of GDP is taken from the World Bank's *World Development Indicators*. This is only consistently available 1990 onwards, and missing data are interpolated using first-observation-carried-back for years prior to 1990.

Health Institutions

We use the following dummy variables:

- EDL = 1 if the country has adopted an Essential Drug List
- NDP =1 if the country has adopted a National Drug Policy
- NF = 1 if the country has adopted a National Formulary

Each of these variables varies across countries and time, and were taken from sources listed in Lanjouw (2005).

Local Technical Capacity

Chemicals Patents is a count of U.S. patents (in 10,000s) by application date in any of the IPC classes corresponding to chemical engineering and manufacturing, as indexed by the American Chemical Society. These include Pesticides, Medicinal Preparations, Chemical Methods and Processes, Inorganic Chemistry, Fertilizers, Organic Chemistry, Macromolecules, Dyes and Paints, Petrochemicals, Soaps and Oils, Beverages and Vinegar, Microbiology and Fermentation, Sugar, and Analyzing Materials; plus Chemical or Physical Laboratory Apparatus, Biocides and Pest Repellants, and Apparatus for Enzymology or Microbiology. This count is constructed for each country/year, based on the country of the inventor(s) listed on the patent, and then converted to a stock using a 15 percent depreciation rate and an assumed pre-sample growth of 10 percent to initialize the stock. If a patent has multiple inventors listed, we count the patent in each of the listed countries.

Governance

Rule of Law and Regulatory Quality index values and rank order (for 181 countries) published in World Bank, *Worldwide Governance Indicators* for 1996, 1998, 2000, 2002 (not available before 1996). We use first-observation-carried-back for years prior to 1996, then last-observation-carried-forward.

Instrumental Variables

Political_Constraints: a measure of credible policy commitment (the degree of political constraints on policy change). It is derived from a spatial model of political interaction and is based on the number of independent veto points in the different branches of the political system and the distribution of political preferences both across and within these branches. Higher values represent greater political constraints (and thus greater policy commitment). For details see Henisz (2000).

Executive_Orientation: a dummy variable that codes whether the executive comes from a right, left or center party with respect to its orientation on economic policy. Source: World Bank Database of Political Institutions: Changes and Variable Definitions (Philip Keefer, December 2009).

Ethnolinguistic_diversity: a measure commonly used as an indicator of difficulty in reaching and committing to political decisions. For details, see La Porta et al. (1999).

Legal_Origin: The historical origins of the legal system for each country is coded as either common law (U.K.), French law, German law, Socialist, or Scandinavian. For details, see La Porta et al. (1999).

Regional Trade Agreements (RTA): he cumulative number of regional trade agreements that the country has entered as of a given year. hese data were compiled from Table 3 of Baier and Bergstrand (2007), supplemented with information from the WTO's online Regional Trade Agreements Information System (RTA-IS). We thank Keith Head for providing a clean version of these data.

All of these instruments vary across countries and over time, with the exception of Legal_Origin.

Ancillary Regressions for Policy Regime Choice

Table A.3 reports the FIML parameter estimates for the price controls and patent policy regime equations. A Probit is used for price controls (=1 if price controls are in place in a given country/year). Ordered Probits are used for process and product patent regimes, ordered by increasing duration (the reference category is no protection). The regressions include the instruments and all covariates from the launch equation reported in the body of the paper. A random country effect is included in all equations with the coefficient normalized in the launch equation.

We present the results for two sets of instruments (labeled narrow and broad). The narrow set includes two instruments: 1) *Political_Constraints*, which measures the degree to which voting rights within the political structure constrains policy change (this is used in the political science literature as a proxy for credible policy commitment; higher values correspond to greater commitment); and 2) *Executive_Orientation*, coded as Left, Right or Center based on the ruling party with respect to its orientation on economic policy (Center is the reference category). The second, broad set includes the first two instruments plus three additional ones: 1) *Ethnolinguistic_diversity*, commonly used in the economics and political science literature as an indicator of difficulty in reaching and committing to political decisions; 2) *Legal_Origin*, coded as UK (common law), French law, German law, or Socialist/Other (the reference category); and 3) *RTA* which is the cumulative number of regional trade agreements that the country has entered. With the exception *of Legal_Origin*, all of the instruments vary both across counties and time.

Columns (1)-(3) are based on the narrow set of instruments; columns (4)-(6) use the broader set. The instruments are all statistically significant both individually and jointly (p-values < 0.001 in all cases). We briefly summarize the qualitative results for the instruments as follows. Price controls are more likely when there are weaker *Political_Constraints* (less policy commitment), a left-leaning *Executive_Orientation*, French legal origins (followed by common law countries), greater *Ethnolinguistic_diversity*, and (weakly) higher RTA indicating greater trade openness. Process patent protection is more likely to be longer when there are weaker *Political_Constraints*, a centrist *Executive_Orientation* (both Left and Right- leaning executive orientation favor shorter protection), German legal origins (followed by UK and French), lower *Ethnolinguistic_diversity*, and higher *RTA*. Finally, product patents are longer when there are weaker *Political_Constraints*, a centrist *Executive_Orientation*, German (followed by UK and French) legal origins, higher *Ethnolinguistic_diversity*, and higher *RTA*.

The noteworthy conclusions from the other covariates are: larger countries (population and GDP/capita), and those with greater income inequality and older populations are less likely to have price controls and more likely to have longer process and product patent protection. Countries which have adopted the Essential Drug List are less likely to have price controls and more likely to have longer patent regimes, while those with a National Formulary are more likely to have both price controls and longer patent regimes. Finally, the coefficient on the random country effect is negative in the price control equation, and positive in the process and product patent equations. Recalling that the coefficient is normalized in the drug launch equation, this indicates that unobserved country factors that promote earlier launch of new drugs also make it more likely that the country adopts longer process and patent policy regimes, but less likely to adopt strong price controls.

While these results are descriptively intriguing, we emphasize that these regressions do not have a structural interpretation because they are not based on any formal model of how price regulation and patent policy are determined. The economics and political science literature has not reached any consensus on how to model policy-making in general (including these policy regimes), and the challenges to formulate such models that are applicable to widely diverse countries are formidable.

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Table A.1. Summary Statistics (country-year observations)

Variables	Mean	Std. Dev	Minimum	Maximum
Policy Regimes				
Short_Process	0.11	0.31	0.00	1.00
Medium_Process	0.22	0.42	0.00	1.00
Long_Process	0.60	0.49	0.00	1.00
Short_Product	0.07	0.25	0.00	1.00
Medium_Product	0.16	0.37	0.00	1.00
Long_Product	0.59	0.49	0.00	1.00
Propatent Index	0.42	0.23	0.00	1.00
Price Controls	0.40	0.49	0.00	1.00
Health Institutions				
National Drug Policy	0.82	0.39	0.00	1.00
Essential Drug List	0.74	0.44	0.00	1.00
National Formulary	0.83	0.38	0.00	1.00
Other Variables				
Population (millions)	49.44	119.05	0.41	1034.17
GDP/cap (thousands)	12.58	8.83	1.12	48.59
Health/GDP (percent)	4.48	8.83	0.20	15.78
Gini Coefficient	39.25	10.05	19.49	63.00
% Pop Age 65+	8.40	4.95	1.40	18.07
Bureaucratic Quality	67.96	24.71	16.67	100.00
Rule of Law index	4.25	1.50	1.00	6.00
Chemical patents (10,000s)	0.10	0.46	0.00	5.20

NOTES: 1,228 observations on variables measured at the country-year level. Up to 76 countries observed 1983-2002. Data form an unbalanced panel based on availability of launch data, with not all countries observed for the full time period.

Table A.2: Policy Regimes and Drug Launches by Country

Country	Product Patent Regime	Process Patent Regime	Price Control Regime	Percent of Drugs Launched Within 5 Yrs	Percent of Drugs Launched & FDA approved
Argentina	N,S,M,N	S,M,L	S,N	45.3	56.5
Australia	M,L	M,L	N	27.3	38.2
Austria	N,L	L	S	44.4	58.0
Bangladesh	M	M	N	9.7	11.0
Belgium	L	L	S	36.3	47.5
Benin	S,L	S,L	S	12.2	14.0
Bolivia	L	L	N	8.6	10.1
Brazil	N,M,S	N,S	S,N	31.6	42.0
Bulgaria	L	L	N	18.3	21.1
Cameroon	S,L	S,L	S	12.2	14.0
Canada	L	L	N	37.5	54.6
Chile	M	N,M	N	28.8	36.6
Colombia	N,M,L	N,M,L	S,N	31.5	42.5
Costa Rica	N,S,L	L,S,L	N	28.5	36.6
Cote D'Ivoire	S,L	S,L	S	12.2	14.0
Czech Republic	L	L	N	41.9	46.9
Denmark	M,L	M,L	N	44.9	59.4
Dominican Republic	M	M	N	21.3	26.8
Ecuador	N,M,L	M,L	S	22.1	28.5
Egypt	N	M	S	10.3	13.8
El Salvador	M	M	N	28.5	36.6
Finland	L,N,L	L	S,N	43.5	59.1
France	L	L	S	37.5	44.2
Gabon	S,L	S,L	S	12.2	14.0
Germany	L	L	N	55.0	67.9
Greece	M,L	M,L	S	35.7	46.8
Guatemala	N	M,S	S,N	28.5	36.6
Guinea	S,L	S,L	N	12.2	14.0
Honduras	L,M	L,M	N,S	28.5	36.6
Hong Kong	L	L	N	27.7	37.3
Hungary	N,L	L	N	36.6	41.2
India	N	S	S,N	8.2	10.9
Indonesia	N,M,L	N,M,L	N	19.5	25.9
Ireland	L	L	N	38.5	50.8
Israel	L	L	S	24.0	34.0
Italy	L	L	S,N	52.3	60.3
Japan	L	L	N	31.9	34.4
Jordan	L	L	S	12.9	15.8
Kuwait	N,L	S,L	S	21.5	25.4
Latvia	L	L	N	20.1	23.2
Lebanon	N,L	M,L	S	19.7	22.3
Luxembourg	L	L	S	25.4	29.5
Malaysia	L,M	L,M	N	20.2	27.1
Mexico	N,L	N,L	N,S,N	37.4	48.7
Morocco	L,N,L	N,L	S	13.7	16.1
Netherlands	L	L	N	39.4	50.4
New Zealand	L	L	N	28.8	39.0
Norway	L	L	N	47.0	53.5
Pakistan	M,L	M,L	S	14.8	16.9
Panama	M	M	N,S	28.5	36.6
Paraguay	N	M	S	19.4	23.7
Peru	N,M,L	N,M,L,N	S,N	20.6	26.4
Philippines	L	L	N	31.8	40.4
Poland	L	L	N	34.2	39.6
Portugal	N,L	M,L	N	24.6	28.3
Puerto Rico	L	L	N	48.7	59.6
Russia	L	L	N	14.3	16.7
Saudi Arabia	L,M	L,M	S	13.7	19.5
Senegal	S,L	S,L	N	12.2	14.0
Singapore	L	L	N	25.5	33.3
Slovak Republic	L	L	N	34.4	39.5
Slovenia	L	L	N,S	28.7	33.8
South Africa	L	L	N,S	28.8	39.0
South Korea	M,L	M,L	S,N	42.6	46.9
Spain	N,L	L	S	39.1	47.5
Sweden	L	L	S,N	38.9	53.0
Switzerland	L	L	N	44.4	58.4
Taiwan	L	L	N	28.3	35.1
Thailand	N,L	M,L	N	30.4	40.9
Tunisia	N	L	S	8.2	9.2
Turkey	M,L	M,L	S	25.1	33.5
UK	L	L	N	50.6	66.5
UAE	N	S	N	21.1	25.0
Uruguay	N,M	M	N	37.6	43.9
USA	L	L	N	53.1	80.0
Venezuela	N,M,L	N,M,L	N	24.6	32.1

Price Controls: N=None/Weak S=Strong; Patents: N=None S=Short M=Medium L=Long

Table A.3. Probit and Ordered Probit Regressions for Policy Regimes

Equation	1a	1b	1c	2a	2b	2c
Dependent variable	Price Controls	Proc Pat	Prod Patents	Price Controls	Proc Patents	Prod Patents
Specification	Probit	Ordered Probit	Ordered Probit	Probit	Ordered Probit	Ordered Probit
Political Constraints	-0.728**	-0.631**	-0.401**	-0.239**	-1.702**	-1.914**
	(0.041)	(0.042)	(0.038)	(0.042)	(0.038)	(0.039)
Executive Left	0.346**	-0.227**	-0.244**	0.368**	-0.244**	-0.315**
	(0.018)	(0.021)	(0.024)	(0.022)	(0.025)	(0.027)
Executive Right	0.131**	-0.582**	-0.670**	0.146**	-0.500**	-0.576**
	(0.016)	(0.014)	(0.018)	(0.016)	(0.012)	(0.016)
Ethno-linguistic				0.786**	-0.880**	0.213**
Diversity				(0.046)	(0.031)	(0.035)
Legal Origins						
Germany				-0.038	2.731**	4.346**
				(0.036)	(0.074)	(0.055)
Legal Origins UK				0.545**	1.449**	2.986**
				(0.037)	(0.076)	(0.062)
Legal Origins France				1.358**	0.580**	2.291**
				(0.036)	(0.074)	(0.054)
RTAs				0.002*	0.089**	0.092**
				(0.001)	(0.001)	(0.001)
log(Population)	-0.166**	0.011	0.094**	-0.345**	0.190**	0.394**
	(0.007)	(0.007)	(0.007)	(0.010)	(0.007)	(0.008)
Log(GDP/cap)	-0.602**	0.742**	0.994**	-0.528**	0.503**	1.152**
	(0.021)	(0.016)	(0.018)	(0.029)	(0.018)	(0.020)
Log(Health/GDP)	0.370**	0.253**	0.305**	0.638**	-0.025	0.168**
	(0.016)	(0.015)	(0.015)	(0.019)	(0.016)	(0.016)
Gini Coefficient	-0.053**	0.006**	0.032**	-0.098**	0.057**	0.096**
	(0.001)	(0.001)	(0.001)	(0.002)	-0.001	(0.001)
% Pop Age 65+	-0.076**	0.248**	0.189**	-0.164**	0.187**	0.134**
	(0.004)	(0.003)	(0.003)	(0.005)	(0.004)	(0.005)
Bureaucratic Quality	0.007**	0.016*	0.011**	0.015	0.016*	0.017*
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Rule of Law	-0.203**	0.093**	0.187**	-0.179**	-0.153**	-0.273**
	(0.008)	(0.016)	(0.008)	(0.007)	(0.005)	(0.007)
National Drug Policy	0.396**	-0.132**	0.440**	0.369**	-0.010	-0.359**
	(0.002)	(0.020)	(0.021)	(0.023)	(0.019)	(0.022)
Essential Drug List	-0.200**	0.583**	0.963**	-0.296**	0.317**	0.816**
	(0.018)	(0.021)	(0.022)	(0.019)	(0.021)	(0.025)
National Formulary	0.395	0.354**	0.136**	0.334**	0.448**	0.140**
	(0.018)	(0.021)	(0.026)	(0.020)	(0.019)	(0.026)
Country random	-0.405**	1.140**	1.150**	-0.619**	1.070**	1.490**
effect	(0.009)	(0.012)	(0.012)	(0.013)	(0.009)	(0.015)

NOTES: * significant at 5 percent and ** significant at 1 percent. Heteroskedaticity-robust standard errors are reported in parentheses. Parameter estimates from are FIML estimation of each group of three policy regime equations jointly with a hazard model for drug launch: equations 1a, 1b, 1c were estimated jointly with the model in column 4 of Table 5, and 2a, 2b, and 2c with column 5 in Table 5. In the Ordered Probits, the process and product patent regimes are ordered according to increasing duration (the reference category is no protection). The last coefficient is on the country random effect which is common to all three equations (and the hazard of launch equation not reported here).